Understanding Anthracyclines: Synthesis of a Focused Library of Doxorubicin/Aclarubicin - Inspired Structures

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Understanding Anthracyclines: Synthesis of a Focused Library of Doxorubicin/Aclarubicin - Inspired Structures

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Luck is the residue of design

- *John Milton*

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List of Abbreviations

Ac	acetyl
AIBN	azobisisobutyronitrile
Alloc	allyloxycarbonyl
app.	apparent
aq.	aqueous
$Ag(DPAH)_2$	silver(II) bis-(hydrogen dipicolinate)
b	broad
b.r.s.m.	based on recovered starting material
Bz	benzoyl
cat.	catalytic
CEL	conformational energy landscape
CoA	coenzyme A
cod	1,5-cyclooctadiene
COSY	correlation spectroscopy
d	doublet
dd	doublet of doublets
ddd	doublet of doublets of doublets
ddt	doublet of doublet of triplets
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DIPEA	diisopropylethylamine; Hünigs base
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dq	doublet of quartets
DSB	double-stranded break
dt	doublet of triplets
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
dtt	doublet of triplet of triplets
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
eq	molar equivalents
FDA	US Food and Drug Administration

HSQC	heteronuclear single-quantum coherence spectroscopy
IDCP	iodonium di-*sym*-collidine perchlorate
J	coupling constant (Hz)
K_{222}	4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane
LC-MS	liquid-chromatography mass spectrometry
m	multiplet
Ms	methylsulfonate
M.S.	molecular sieves
NDMBA	*N,N*-dimethylbarbituric acid
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
o.n.	overnight
OPMP	*p*-methoxyphenolate
Ph	phenyl
Phen	3,4,7,8-tetramethyl-1,10-phenanthroline
PMB	*p*-methoxybenzyl
pNBz	*p*-nitrobenzoyl
ppm	parts per million
pyr.	pyridine
q	quartet
qd	quartet of doublets
quant.	quantitative
ROS	reactive oxygen species
rt	room temperature
s	singlet
SAR	structure-activity relationship
sat.	saturated
Su	succinimide
t	triplet
TBABr	tetra-*n*-butylammonium bromide
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBSOTf	*tert*-butyldimethylsilyl trifluoromethanesulfonate
td	triplet of doublets
TES	triethylsilyl
Tf	trifluoromethylsulfonate
TFAc	trifluoroacetyl

Chapter 1

Introduction and outline

In the 1950s, the anthracycline daunorubicin (**1**, Figure 1) was isolated from a soil sample found in the area of Castel del Monte, a castle in Italy.[1] Daunorubicin was produced by a strain of the actinobacterium *Streptomyces peucetius* and was initially studied for its antibiotic properties. It was soon found that daunorubicin possessed good activity against murine tumors after which it entered clinical trials as a drug for the treatment of various hematological cancers in the 1960s. In spite of the discovery of fatal cumulative cardiotoxicity as a side-effect of this drug 1967,[2] it received FDA approval in the United States of America in 1972.[3] In 1969, doxorubicin (**2**), also known as adriamycin, was isolated from a culture of *Streptomyces peucetius* var. *caesius*[4]. Doxorubicin showed to be an even more potent anti-cancer drug than daunorubicin, and also to have a broader spectrum of activity against a variety of cancers[5] and was FDA approved in the United States only 5 years later.[6]

Daunorubicin (**1**) and doxorubicin (**2**) differ only in the presence or absence of a hydroxyl group on the 14-position.[7] Both contain four fused rings, three of which comprise an anthraquinone moiety. The individual rings in these tetracyclic systems are commonly referred to as the A, B, C and D rings according to the nomenclature proposed by Brockmann (Figure 1).[8] Their 7-position is decorated with an α-L-daunosamine glycoside. The presence of this sugar moiety is essential for its anti-cancer activity, as the aglycones of daunorubicin and doxorubicin (termed daunomycinone and doxorubicinone, respectively) were shown to have no anti-tumor activity.[9] Different from daunorubicin and doxorubicin, aclarubicin (**3**) contains a trisaccharide with an α-L-rhodosamine (*N,N*-dimethyldaunosamine) at the reducing end, connected to an α-L-oliose (2-deoxy fucose) and an α-L-cinerulose.

Structural differences between anthracyclines **1**-**3** can be divided into three categories: oxidation/substitution pattern on the tetracycle portion, variation in the sugar moiety/moieties and the substitution pattern on the amine.

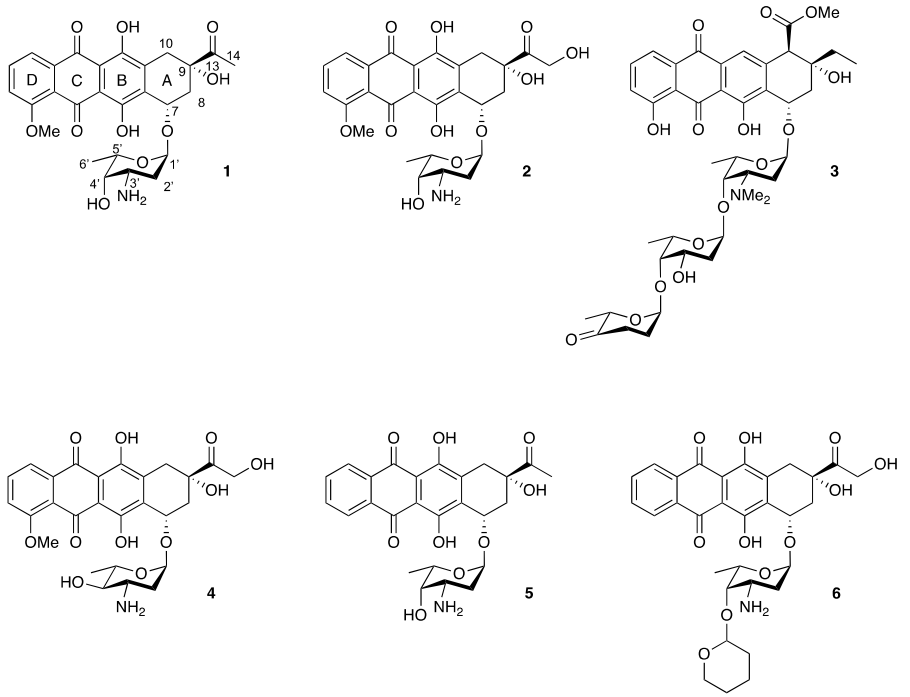


Figure 1. Structures of clinically used anthracyclines daunorubicin (**1**), doxorubicin (**2**), aclarubicin (**3**) epirubicin (**4**), idarubicin (**5**) and pirarubicin (**6**).

The most important anthracyclines currently in the clinic are doxorubicin (**2**), daunorubicin (**1**), aclarubicin (**3**), epirubicin (**4**), idarubicin (**5**) and pirarubicin (**6**). Aclarubicin (**3**, Figure 1) was isolated from the culture broth of *Streptomyces galilaeus* in 1979 by Oki *et al*.,[10] who elucidated the structure of this and related anthracyclines shortly thereafter.[11] It is commonly used for the treatment of various cancers in China and Japan, but not in the rest of the world.[12] This despite the finding that aclarubicin is about tenfold less cardiotoxic than doxorubicin.[13]

Epirubicin (**4**) is the 4'-epimer of doxorubicin, positioning the hydroxyl group on the sugar ring equatorially instead of axially. It has a comparable anti-tumor activity to doxorubicin, but causes fewer side effects in certain treatment regimens, in particular lower cardiotoxicity at comparable dose.[9] This allows for epirubicin to be used at higher doses, without increasing the incidence of heart damage. It was initially prepared through glycosylation of the appropriately protected L-acosamine donor, but a later

developed method entailed C4'-inversion and 14-hydroxylation on biosynthetic daunorubicin.[14] Idarubicin (**5**) is a semisynthetic product that represents the 4-desmethoxy analog of daunorubicin, and possesses broader-spectrum activity.[15] Epirubicin (**4**) and idarubicin (**5**) are part of a library of 200 doxorubicin variants prepared through chemical synthesis at Farmitalia, the company that discovered doxorubicin and daunorubicin.[16] Pirarubicin (**6**) was developed by Umezawa *et al.* and showed similar antitumor efficacy to doxorubicin.[17] However, it was found to be active against a number of doxorubicin-resistant cell lines. Cellular uptake for pirarubicin is faster than doxorubicin in tumor cells *in vitro* and is now used for head and neck cancer, stomach cancer, upper urinary tract cancer, uterus cancer, ovarian cancer, acute leukemia and malignant lymphoma in Japan.[18]

Through mutation of the enzymes required for anthracycline saccharide biosynthesis and feeding of non-natural glycosyl donors as well as organic synthetic efforts, thousands more such analogs have been prepared, most notably between the early 1980s and early 2000s.[19] Nevertheless, almost fifty years after its discovery, doxorubicin still remains the most used anthracycline in cancer treatments. Its global annual market had reached $800 million by 2015,[20] and is expected to increase even further. Doxorubicin induced cardiotoxicity still severely hampers treatment and an anthracycline that would display less toxicity of the heart, or is more potent and therefore could be used at a lower dose, remains much desired. The recent discovery of histone eviction as a major mechanism of action brings new information regarding the mechanisms of action of anthracyclines, consequently incentive to reinvestigate the exact molecular mechanism.

This Chapter first outlines the mechanisms of action of the anthracycline class of drugs, in addition to side effects that accompany their use. Then, it gives information on the biosynthesis of anthracyclines as well as the chemical synthesis of analogs. Finally, it will provide an overview of the work described in this Thesis.

1.1 Mechanisms of action and side effects of anthracyclines

Since the discovery of daunorubicin (**1**), multiple mechanisms of action for the anthracycline class of anti-cancer drugs have been reported. The most commonly accepted mode of action is the ability of anthraquinone glycosides to inhibit the catalytic cycle of the DNA (un)winding enzyme Topoisomerase II (Topo II). This enzyme plays an important role in the decatenation of intertwined DNA strands, and the relaxation of tension in the DNA strand in front of the replication fork. Topo II does this by creating a break in one of the strands of double stranded DNA, hereby allowing the

second strand to pass and subsequently closing the initial break by religation of the two DNA strand ends. Doxorubicin and daunorubicin bind and inhibit Topo-II in its catalytic steps following initial DNA double-strand break (DSB) by forming a stable DNA-drug complex, preventing religation of the broken strands, ending up with DNA damage.[21] As a result, the cell cycle is arrested, DNA repair processes are activated and p53-mediated apoptosis is induced.[22] At high concentrations, anthracyclines are also able to inhibit Topo-II activity by intercalation into DNA without inducing DNA damage.[23] This intercalation leads to an inability of DNA transcription enzymes to perform their function.[24,25] As demonstrated by Pang *et al*.,[26] aclarubicin (**3**) does not induce DNA DSBs, because it inhibits loading of the DNA strands into the enzyme before it makes a DSB.[27]

Owing to the anthraquinone function present in all anthracyclines, their anti-tumor activity has also been ascribed to the formation of Reactive Oxygen Species (ROS) through this moiety.[28] As depicted in Figure 2, addition of a free electron to this moiety by oxidative enzymes such as NADH dehydrogenase, cytochrome P450 reductase and xanthine oxidase yields a stable semi-quinone radical anion of doxorubicin. This radical can react with molecular oxygen to form superoxides and hydrogen peroxide. Under the agency of iron(II) and iron(III), this will generate hydroxyl radicals through the Fenton reaction.[29] These radicals can cause DNA damage, protein modification and lipid peroxidation.[30,31] However, this effect has only been shown at higher than clinical doxorubicin/daunorubicin concentrations, so its actual *in vivo* effect is still under debate.

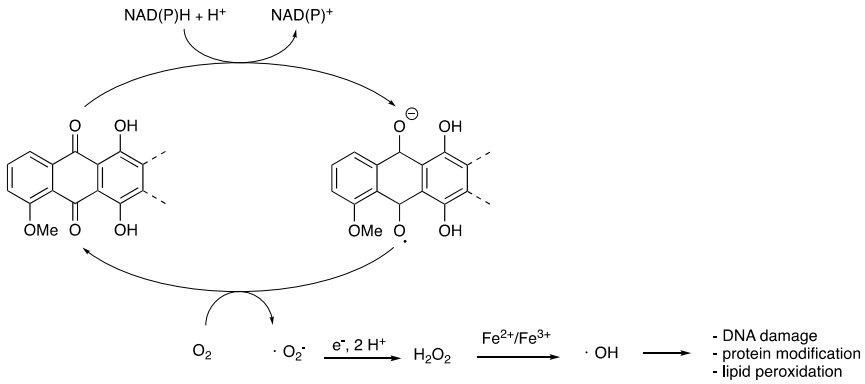


Figure 2. Generation of reactive oxygen species (ROS) as induced by anthracyclines.

A recent work by Pang *et al.*[26] showed that certain anthracyclines are able to evict histones from different areas of chromatin, an effect also known as chromatin damage. Histones are responsible for chromosome organisation at the most basic level and act

as spools around which DNA is wound in compact structures. Chromatin exists either in a loosely packed, also known as euchromatin form, or in a compacted form known as heterochromatin. The open chromatin is in general more transcriptionally available compared to the heterochromatin, which is usually associated with transcriptionally repressed genomic regions. Upon intercalation of the aglycone moiety of doxorubicin into the DNA major groove, the aminosugar sticks out into the minor groove. There, it competes for space with the histone H4 tail, causing destabilization of the complex resulting in its collapse. This results in release of histones from chromatin, chromatin damage and finally cytotoxicity.[32] A model of doxorubicin (**2**) in a histone-wound DNA duplex is depicted in Figure 3. Notable is the finding by Pang *et al.* that doxorubicin possesses both the Topo-II mediated DNA damage activity, as well as the ability to induce histone eviction. The non-anthracycline Topo-II inhibitor etoposide is able to induce DNA damage only, but not histone eviction. Aclarubicin (**3**) was found to be able to evict histones without causing DNA damage. This prompts the notion that the DNA damage ability is not crucial for the anti-tumor activity of anthracyclines and that histone eviction alone might suffice for cytotoxicity. Furthermore, this chromatin damage was found to occur with a certain regiospecificity, that is different for doxorubicin and aclarubicin. Whether this divergence in binding to specific regions within the genome is therapeutically relevant remains to be investigated.[33,34]

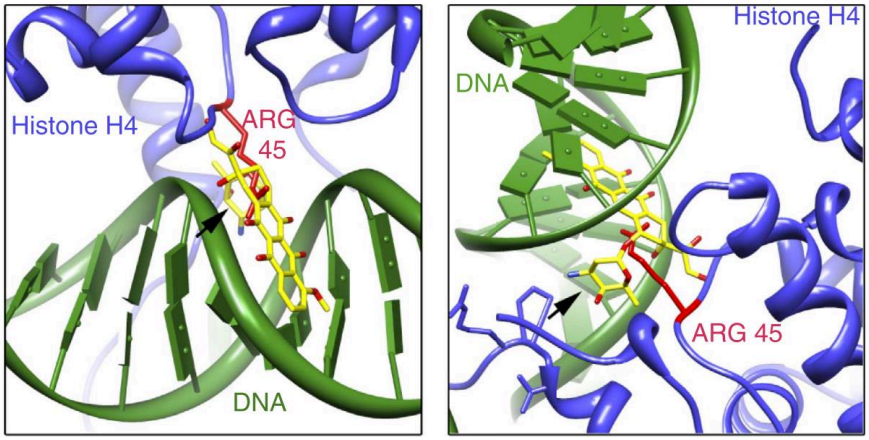


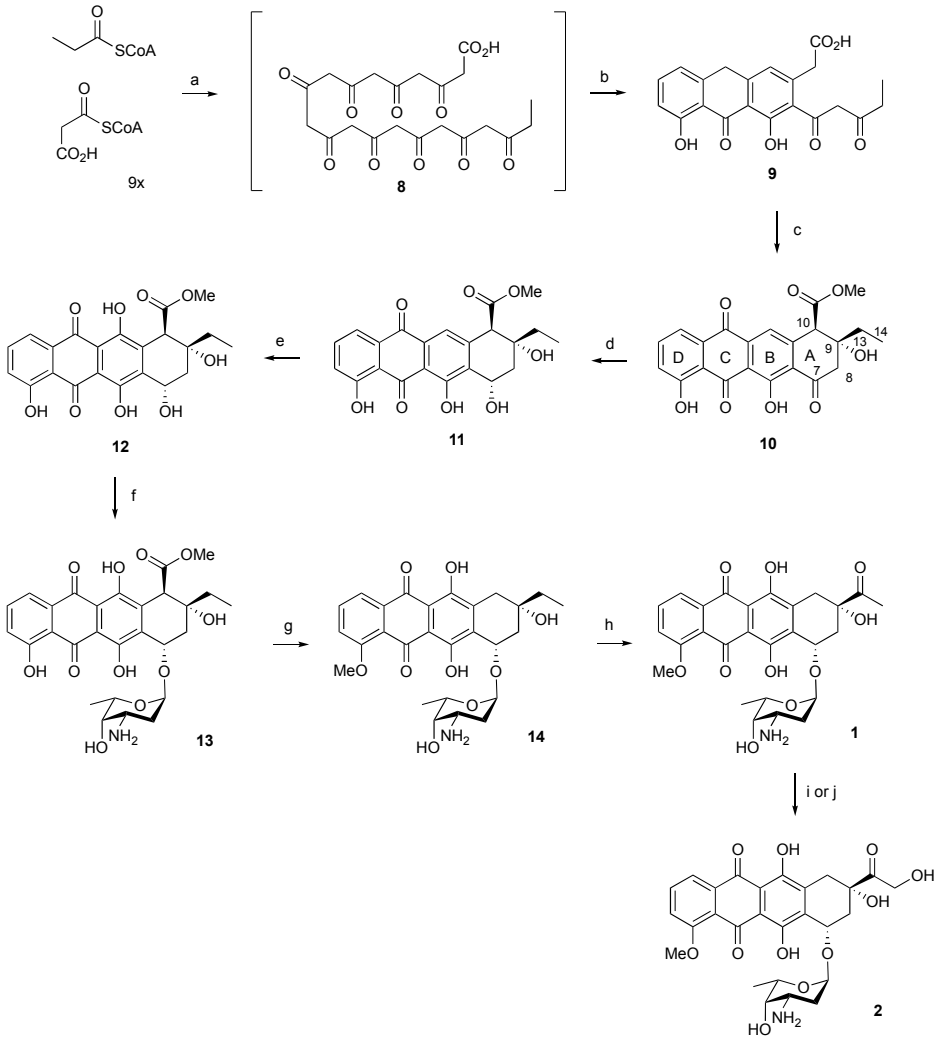
Figure 3. A model of doxorubicin (**2**) intercalation in chromatin, with the aminosugar moiety of doxorubicin competing with histone tail H4 for access to space in the DNA minor groove. Shown is a snapshot of the relevant area of the model under two angles. DNA is visualized in green, doxorubicin in yellow, histone H4 in blue and the H4-arginine residue (at position 45) that enters the DNA minor groove is shown in red.[26]

As with most anti-cancer drugs, the use of anthracyclines comes with a range of adverse effects. Most notable amongst these is the incidence of dose-related cardiotoxicity, an effect that was already uncovered for daunorubicin in 1967.[2] This effect, which is much

more prominent for doxorubicin than aclarubicin, is irreversible and can be lethal, leading patients to require alternative treatment strategies to avoid heart failure.[22,35] ROS formation has been studied as a cause for anthracycline induced cardiotoxicity, but as the co-administration of anti-oxidants failed to ameliorate it, this mechanism appears unlikely.[36] A second well known side effect for most of the anthracyclines is the formation of therapy related tumor formation, often in the form of acute myeloid leukemia.[37] Infertility is another side-effect of this class of drugs.[38] Although the anthracycline drugs are widely used anti-cancer drugs, a clear relation between their biological activities and the side effects is still poorly understood. Therefore, the availability of coherent sets of anthracyclines is of great value to study this. The biosynthetic and synthetic organic preparation of such compound collections is discussed in the upcoming paragraphs.

1.2 On the biosynthesis of anthracyclines

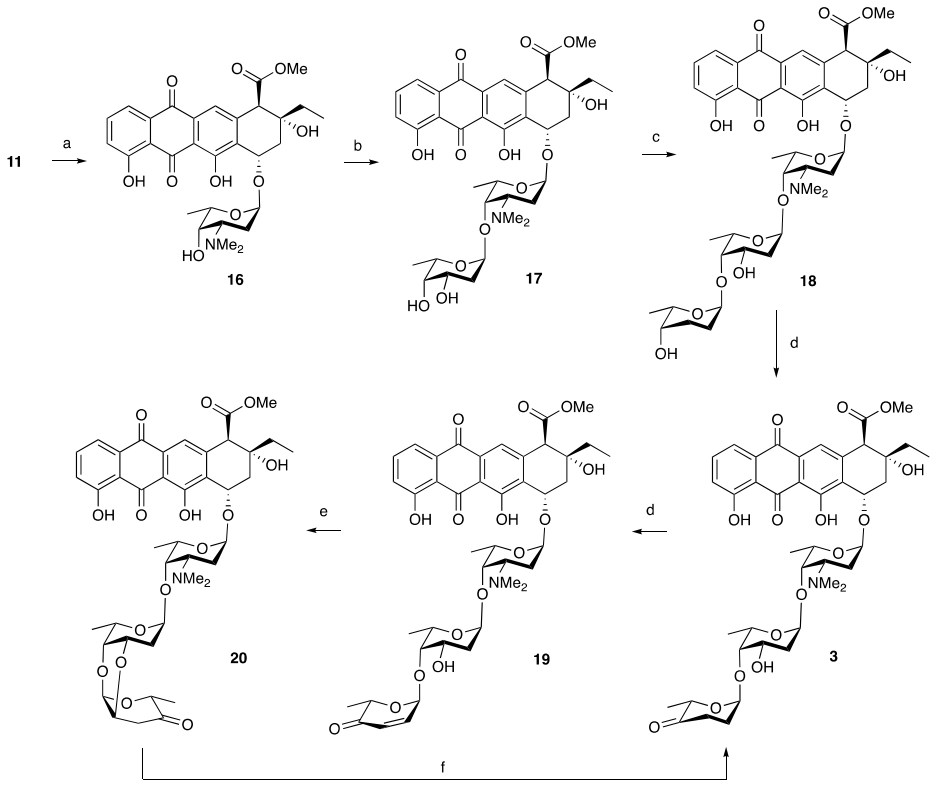
The biosynthesis of daunorubicin and doxorubicin has been extensively optimized to allow for the large-scale production of these drugs by fermentation. Scheme 1 outlines the biosynthetic steps in the production of daunorubicin and doxorubicin. The initial A,B,C,D ring system is produced by a type-II polyketide synthase. Propionyl-CoA is elongated by the sequential decarboxylative addition of nine units of malonyl-CoA to yield 21-carbon polyketide **8**. A sequence of cyclization reactions and other modifications then gives the aglycone found in aclarubicin, aklavinone **11**. This compound is hydroxylated on the C-11 position to give ε-rhodomycinone **12**. Appendage of TDP-daunosamine then delivers rhodomycin D (**13**) as the first anthraquinone glycoside in this biosynthesis. With this sugar in place, several steps take place to transform the aglycone. The C-9 methyl ester is enzymatically demethylated, and decarboxylated by *DnrK* to provide **14**.[39] Oxidation of the C-13 methylene leads to the corresponding ketone, with a final C-4 phenol methylation completing daunorubicin (**1**). Initially, the mutant *Streptomyces peucetius* ATCC 27952[40] was found to produce doxorubicin in small quantities and the enzyme responsible for hydroxylation of C-14 turned out to be the same as the one that is responsible for the C-13 oxidation (*DoxA*). However, the enzyme has a low turnover for this hydroxylation reaction in the wild-type strain. Although some mutants that overexpress *DoxA* were able to double the yield of doxorubicin, complete hydroxylation has not been achieved yet, yielding mixtures of doxorubicin and daunorubicin.[41] Daunorubicin then still needs to be converted to doxorubicin by means of chemical synthesis (bromination of C-14 followed by hydrolysis).[42,43] This complicates the production of doxorubicin and as a result there is still significant attention to the improvement of its production.[44]



Scheme 1. Biosynthesis of daunorubicin and doxorubicin by *S. peucetius*.[45] (a) Assembly of the polyketide by sequential decarboxylative addition of 9 units of malonyl-CoA to propionyl-CoA; (b) Reduction at C-4 and cyclization to form the D, C and B rings; (c) Oxidation at C-12, methylation of the carboxylic acid and Claisen condensation to cyclize the A-ring; (d) Reduction of the C-7 ketone to give aklavinone; (e) Hydroxylation at C-11 to yield ε-rhodomycinone (**13**); (f) Glycosylation on C-7 with TDP-daunosamine; (g) Demethylation of the ester at C-10 by *DnrP*, followed by decarboxylation and C-4 phenol methylation by *DnrK*; (h) Oxidation at C-13 by *DoxA*; (i) Chemical hydroxylation of C-14 by *i.* Bromination of C-14; *ii.* Hydrolysis; (j) Enzymatic hydroxylation at C-14 by enzymatic overexpression of *DoxA*, as in mutant ATCC 27952.[40]

Aclarubicin (**3**) is also produced by means of fermentation, and the biosynthetic steps as performed by *Streptomyces galilaeus* are shown in Scheme 2. The biosynthesis commences with the assembly of aklavinone (**11**), as described before for *Streptomyces*

peucetius.[46] Appendage of the rhodosamine moiety on C-7 gives aclacinomycin T (**16**), which is transformed into aclacinomycin S (**17**) by appending an oliose moiety. Next a rhodinose is attached to the terminal sugar, giving aclacinomycin N (**18**). Oxidation of the terminal 4'''-alcohol to furnish the cinerulose moiety is performed extracellularly by the enzyme *AknOx* and yields aclarubicin (**3**). However, the same enzyme is also able to oxidize the cinerulose C2,C3-bond to yield the corresponding enone aclacinomycin Y (**19**).[47] Cyclization by the addition of the 3"-OH onto the enone functionality of the resulting sugar moiety (which is named aculose) delivers aclacinomycin B (**20**). Upon reuptake into the cell, this compound can be converted back into aclarubicin. In practice, mixtures of aclarubicin, aclacinomycin B and Y are obtained by fermentation, making the purification process of aclarubicin difficult.



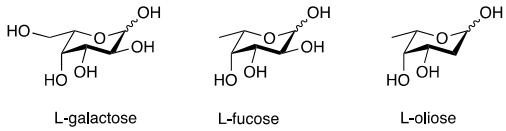
Scheme 2. Biosynthesis of aclarubicin (**3**) by *S. galilaeus*.[46] (a) Glycosylation on C-7 with TDP-L-rhodosamine; (b) Glycosylation on 4'-OH with TDP-L-oliose; (c) Glycosylation on 4''-OH with TDP-L-rhodinose; (d) Oxidation of 4'''-OH by *AknOx*, or oxidation of 2'''-3''' by the same enzyme; (e) Cyclisation between the enone and C3"-OH; (f) Cleavage of the bond between 3"-OH and C2'''.

The synthesis of coherent sets of anthracyclines to facilitate the elucidation of the structure-activity relationships of doxorubicin (**2**) and aclarubicin (**3**) would require careful tailoring of mutant enzymes for each of the individual desired analogs. Therefore, a divergent synthetic strategy was instead chosen to obtain such sets of compounds. General considerations in the organic synthesis of anthracyclines, as well as examples of their (semi)synthesis are discussed in the upcoming paragraphs.

1.3 Organic synthesis of anthracyclines

1.3.1 Challenges in the preparation and glycosylation of deoxy glycosides

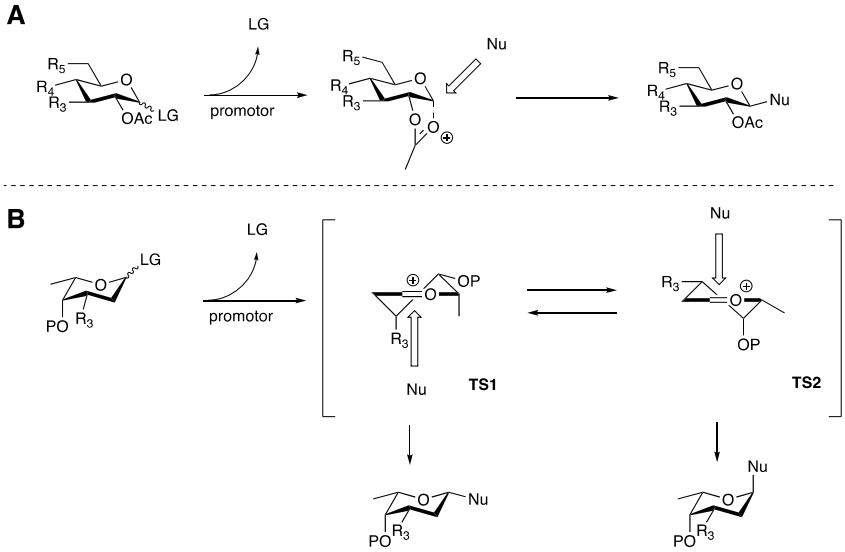
As shown in Figure 1, the sugars present in anthracyclines can all be characterized as 'deoxy' sugars: they lack one or more hydroxyls when compared to the more common sugars (such as glucose, mannose, galactose). Deoxy glycosides are widely found as components in antibiotics and anti-cancer agents, originating from bacterial sources. These compounds show immense variation as well as structural complexity and have therefore been subject of many total synthesis efforts.[48] The lacking hydroxyl group(s) are substituted for nitrogen substituents (primary/secondary/tertiary amines, acetamides, nitro groups) or by hydrogen. Quaternary stereocenters featuring amine or hydroxyl groups may also be present. These differences when compared to fully oxygenated saccharides have a tremendous effect on their synthetic preparation and glycosylating properties of their corresponding glycosyl donors.



L-galactose L-fucose L-oliose

Figure 4. Structures of L-galactose, L-fucose and L-oliose.

The structure of L-galactose, its 6-deoxy variant L-fucose and 2,6-dideoxygenated L-galactose (L-oliose) are depicted in Figure 4. Because fewer electron-withdrawing oxygen substituents are present on the pyranose ring going from L-galactose to L-fucose and finally L-oliose, the electron density on the ring increases, which leads to higher reactivity of the corresponding glycosyl donors. For the same reason, the glycosidic linkages of deoxy sugars are more labile towards (Lewis-)acidic conditions than their fully oxygenated counterparts. These effects are especially pronounced when the deoxygenated positions are close to the anomeric center (*i.e.* at C2 and C6).



Scheme 3. A) Formation of a β-glycosidic bond through neighboring group participation for glucose donors. B) Rationale of the stereochemical outcome in the glycosylation of 2-deoxy fucosyl donors.

The lack of a 2-substituent strongly impacts the stereoselectivity of the glycosylation of 2-deoxy glycosyl donors. While anchimeric assistance of a C2 participating group can be called upon for the stereoselective construction of 1,2-*trans* glycosidic bonds in carbohydrates with a C2-oxygen or nitrogen substituent (Scheme 3A), this type of stereocontrol cannot be applied to C2-deoxy glycosides, present in the anthracyclines. Because of the higher reactivity of 2-deoxy glycosyl donor, glycosylations take place through the intermediacy of species bearing more carbocation character, *i.e.* oxocarbenium ion like species. The reactivity of these latter species is governed by their overall shape, which is dictated by the nature of the groups on the 3-, 4- and 6-position (See Scheme 3). Factors such as the solvent, temperature and the nature of the nucleophile strongly influence the outcome of the glycosylation reactions.

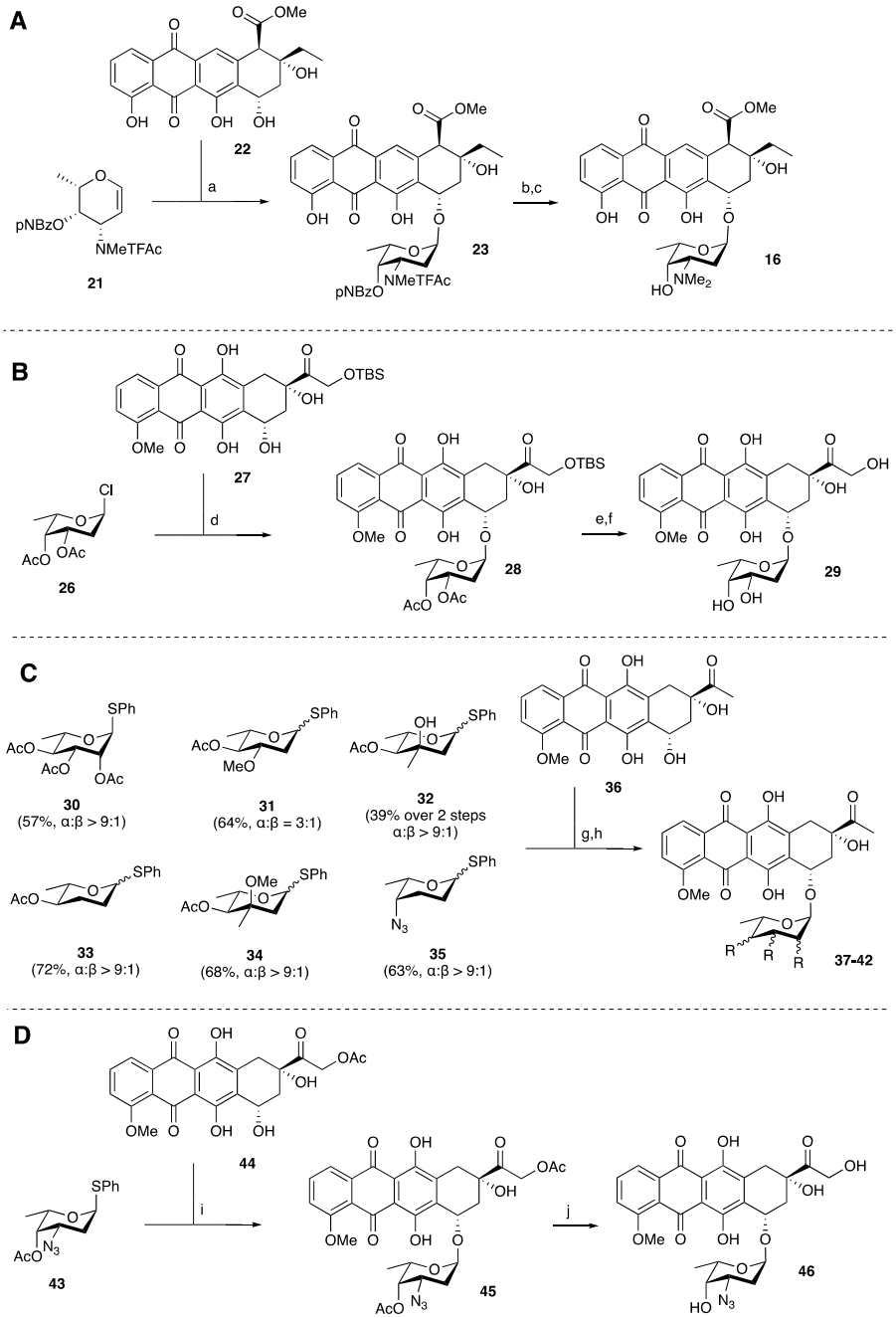
The scarcity of many of the deoxygenated monosaccharides in nature is reflected in the costs and efforts required for their preparation. Only a few are commercially available, and they become significantly more expensive as their natural abundance diminishes. Although they can be synthesized from more abundant sugars, these routes of synthesis are normally quite lengthy. Depending on the deoxygenation site, a multitude of methods has been developed to prepare the desired ring-substitution motif. Examples include tin-mediated radical deoxygenation of halides,[49] formation of glycals from glycosyl bromides,[50] Ferrier-rearrangement of glycals to obtain 2,3-dideoxyglycosides,[51] Barton-McCombie deoxygenation,[52] hydrogenation of ring-

substituted thiolates or selenides[53] and these methods will be elaborated upon in Chapter 2-5 of this Thesis.

1.3.2 Glycosylation strategies in the synthesis of anthracyclines

Since the discovery of doxorubicin and aclarubicin, the synthesis of anthracyclines has gathered considerable attention. The formation of the α-glycosidic linkages in anthracyclines is no trivial matter but has nevertheless been accomplished by the use of several donor-promoter systems, some of which are highlighted in this paragraph. Pearlman *et al*. reported the synthesis of aklavin (**16**) and *N*-demethylaklavin (**24**) in 1981 (Scheme 4A).[54] They prepared glycal donor **21** from daunosamine and were able to stereoselectively glycosylate this to aklavinone (**22**) using a catalytic amount of *p*-toluenesulfonic acid to yield **23**. Treatment with excess sodium methoxide removed the *N*-trifluoroacetyl and *p*-nitrobenzoate groups, which was followed by Borch conditions (aq. CH_2O, $NaBH_3CN$, AcOH) to yield aklavin (**16**). A few years later, Horton *et al.* prepared 3'-desamino-3'-hydroxydoxorubicin **29** (Scheme 4B).[55] Activation of L-oliosyl chloride **26** under Koenigs-Knorr conditions ($HgBr_2$, HgO) in the presence of 14-TBS-doxorubicinone **27** afforded protected anthracycline **28**. Zemplén deacylation followed by treatment with tetra-*n*-butylammonium fluoride (TBAF) afforded hydroxyrubicin **29**. Wang *et al*. prepared the set of daunorubicin analogs **37**-**42** with uncommon deoxysugars in 2005 (Scheme 4C).[56] Thioglycosides **30**-**35** were activated by $AgPF_6$ in the presence of TTBP (2,4,6-tri-*tert*-butylpyrimidine) and daunorubicinone **36** to generate the daunorubicin glycosides, which were deacylated to yield the corresponding daunorubicin analogs in varying yield and stereoselectivity. The same group prepared 3'-azidodoxorubicin (**46**) (Scheme 4D).[57] In this case, thioglycoside **43** was activated by *N*-iodosuccinimide (NIS) and a catalytic amount of triflic acid in the presence of **44** to yield the target compound **46** after deacylation. Weil *et al.* realized the preparation of the same compound by one-step diazotransfer on doxorubicin.[58]

In 1990, the group of Danishefsky reported the synthesis of the natural product anthracycline "ciclamycin 0" (**56**) shown in Scheme 5A.[59] Their synthesis features the first fully synthetic oligosaccharide to be glycosylated to an anthracycline aglycone, using a strategy relying on the activation of glycals by means of iodonium dicollidinium perchlorate (IDCP).

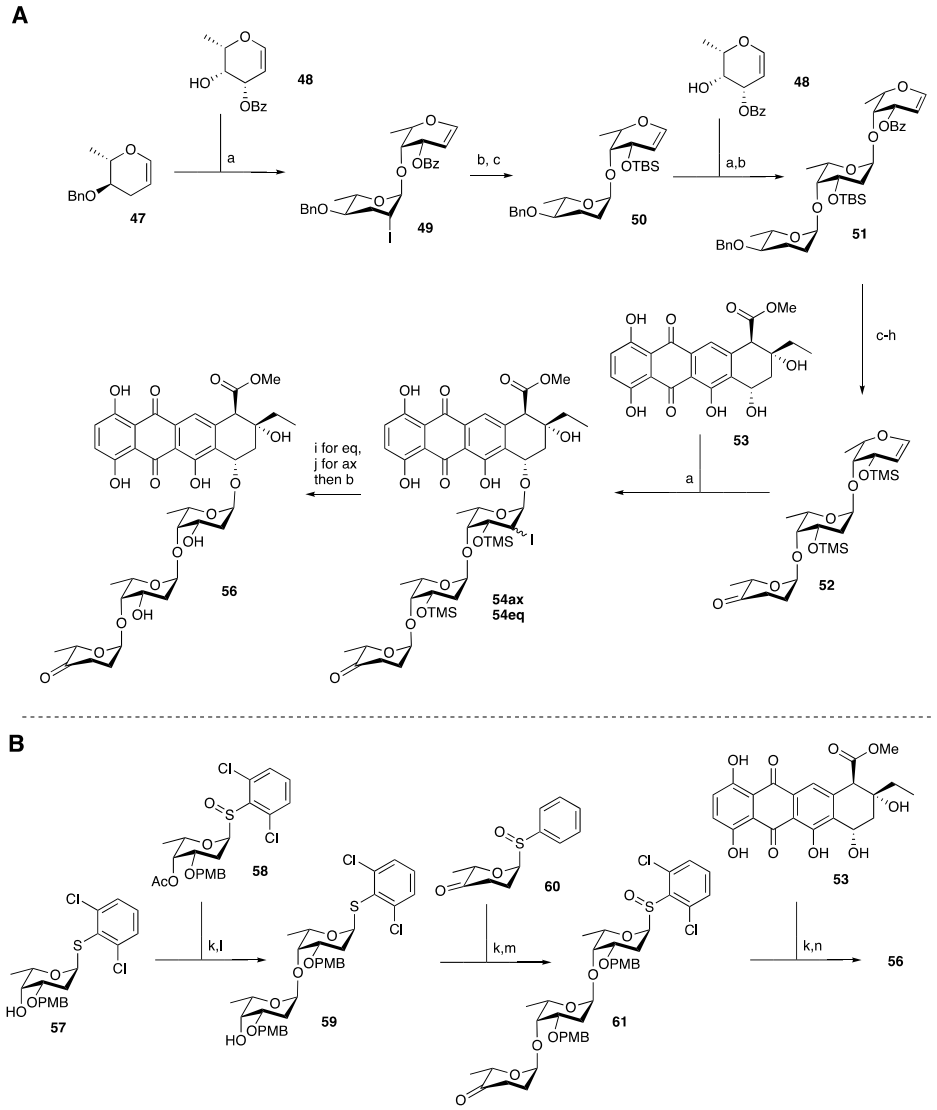


Scheme 4. Selected syntheses of monosaccharidic anthracyclines. *Reagents and conditions:* (a) *p*-toluenesulfonic acid, benzene, 50 °C, 80%; (b) NaOMe, MeOH, -20 °C; (c) aq. CH_2O, $NaBH_3CN$, AcOH; (d) HgO, $HgBr_2$, DCM, 83%; (e) NaOMe, MeOH, 88%; (f) TBAF, pyr., THF, DCM, 83%; (g) $AgPF_6$, TTBP, DCM, 0 °C, 57-72% (>9:1 – 3:1 α:β); (h) NaOH, THF, H_2O, 39-75%; (i) NIS, TfOH, DCM, 0 °C, 64%; (j) NaOH, THF, H_2O, 70%.

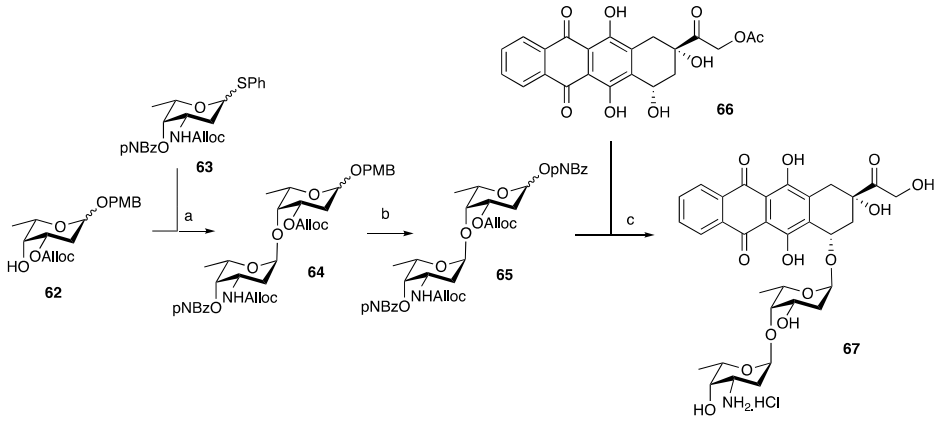
In this vein, glycal **47** was chemoselectively coupled to glycal **48** to afford the corresponding 2'-iodo disaccharide glycal **49**. The iodide was then reductively removed using Ph_3SnH. Switching the benzoyl group for a TBS group gave disaccharide **50**, which could now be activated by IDCP. Doing so in the presence of acceptor **48** gave the corresponding trisaccharide **51** after reductive removal of the 2'-iodide. Protecting group manipulation and oxidation of the terminal 4-hydroxyl gave trisaccharide donor **52**. Treatment of a mixture of this donor and ε-pyrromycinone **53** with IDCP gave 60% of the α,α,α-linked trisaccharide anthraquinone as a mixture of the axial and equatorial 2'-iodide. Removal of the TMS ethers and final reductive removal of the iodide afforded ciclamyin 0 (**56**).

In 1999, Kahne's group also prepared ciclamycin 0, by means of glycosylations using glycosyl sulfoxide donors, as depicted in Scheme 5B.[60] Initially the authors tried to use benzyl ethers in the synthesis of this compound, but noted that the hydrogenolytic conditions used for the deprotection also cleaved the glycosidic linkage to the benzylic aglycon. To synthesize the trisaccharide, sulfoxide **58** was activated with triflic anhydride in the presence of oliosyl acceptor **57**, DTBMP and 4-allyl-3,4-dimethoxybenzene as sulfenyl scavenger to afford disaccharide acceptor **59** after reductive deacylation. In the same manner, cineruloside **60** was appended to finish the trisaccharide motif. The 'latent' reducing end thioglycoside was then oxidized by means of dimethyldioxirane to afford the corresponding sulfoxide donor **61**. Adding this donor to a mixture of triflic anhydride, DTBMP and 4-allyl-3,4-dimethoxybenzene as well as aglycone **53** afforded the protected anthracycline stereoselectively in good yield. Final oxidative removal of the PMB groups by action of excess DDQ furnished ciclamycin 0.

The pharmaceutical company Menarini Richerche reported the synthesis of a series of doxorubicin-inspired di- and trisaccharides.[61,62] Representative of these is the synthesis of MEN10755, or sabarubicin **67**, which is shown in Scheme 6. Subjection of a mixture of olioside **62** and daunosaminide **63** to excess IDCP in Et_2O/DCE afforded disaccharide **64**. The reducing end PMB group was then removed oxidatively (ceric ammonium nitrate), after which the resulting lactol was acylated to obtain *p*-nitrobenzoate disaccharide **65**. Activation of this donor with TMSOTf in the presence of 14-acetoxy-4-demethoxydoxorubicinone (**66**) afforded sabarubicin (**67**), after deprotection of the acetate and Alloc groups.



Scheme 5. Syntheses of trisaccharidic anthracycline ciclamycin 0 (**56**) by the groups of Kahne and Danishefsky. *Reagents and conditions:* (a) *i.* IDCP, DCM, 0 °C 66% for **49**, 54% for **51**, 60% for **54**; (b) Ph_3SnH, AIBN, benzene, 80 °C, 86% from **49**, 93% for **51**, 55% (77% B.R.S.M) from **54eq**, 72% (98% B.R.S.M) from **54ax**; (c) *i.* $LiAlH_4$, Et_2O, 0 °C ; *ii.* TBSCl, imidazole, DMF, 60% over 2 steps for **50**, 79% over 2 steps from **51**; (d) *i.* Li, NH_3(l), -78 °C ; *ii.* Ac_2O, Et_3N, DMAP, 87% over 2 steps; (e) TBAF, THF, quant.; (f) TMSCl, Et_3N, DMAP, DCM, 0 °C, 99%; (g) $LiAlH_4$, THF, 0 °C, 82%; (h) Dess-Martin periodinane, $NaHCO_3$, DCM, 95%; (i) *i.* AcOH, THF, MeOH, 97%; *ii.* TBAF, THF, 41% (72% B.R.S.M); (j) AcOH, THF, MeOH, 79%; (k) Tf_2O, DTBMP, 4-allyl-3,4-dimethoxybenzene, DCM, 81% from **57**, 68% (5:1 α:β) from **59**, 75% from **61**; (l) $LiAlH_4$, Et_2O, 0 °C, 92%; (m) dimethyldioxirane, -72 °C to -42 °C, 90%; (n) DDQ, DCM, H_2O, 60%.



Scheme 6. Synthesis of the anthracycline disaccharide sabarubicin (**67**) at Menarini Richerche. *Reagents and conditions:* (a) IDCP, Et_2O, DCE, 90%; (b) *i.* $(NH_4)_2Ce(NO_3)_6$, MeCN, H_2O; *ii.* pNBzCl, pyr., 0 °C, quant. over 2 steps; (d) *i.* TMSOTf, DCM, Et_2O, -10 °C; *ii.* K_2CO_3, MeOH, H_2O; *iii.* $Pd(PPh_3)_4$, Me_2NTMS, TMSOAc, DCM; *iv.* aq. HCl, 77% over 4 steps.

1.4 Outline of this Thesis

Since the discovery of daunorubicin in the 1950s, a multitude of (bio-)synthetic analogs have been prepared in an attempt to find improved, less cardiotoxic anthracyclines. Unfortunately, this has not resulted in a significantly improved anti-cancer anthracycline, and the molecular understanding of the mode of action of this class of drugs remains relatively poor. Uncovering histone eviction as an important mode of action of anthracyclines has provided a new incentive to investigate the structure-activity relationships of this class of anti-tumor drugs in detail. The research described in this Thesis focuses on the design and preparation of coherent sets of analogs that combined may inform on the molecular mechanism behind the various biological activities displayed by anthracyclines as (cardiotoxic) antitumor agents. Ultimately, the synthesized compounds, and the biological studies executed within the Chemical Immunology Department at the Leiden University Medical Center, may inform on how to 'separate' the different biological activities by the design of tailored doxorubicin/aclarubicin analogs and unveil how cardiotoxicity can be prevented while maintaining tumor cell toxicity. Possibly, new biological activities, including DNA-sequence (regio)-selective targeting, can be identified, which may lead to new therapeutic indications. The biological studies will be reported in a Thesis by Sabina Y. van der Zanden, to augment the results in anthracycline design and synthesis described in this Thesis. The Thesis comprises of the four experimental Chapters 2-5, followed by Chapter 6 that looks ahead based on the results obtained so far.

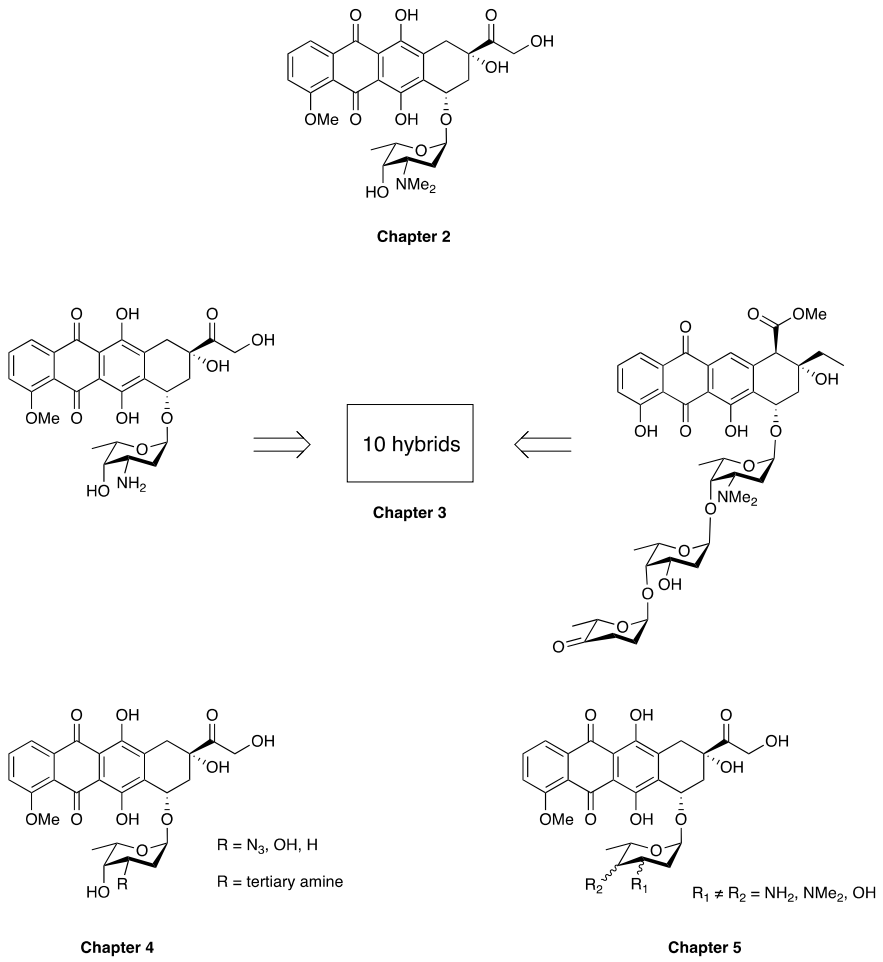


Figure 5. Global overview of the doxorubicin and aclarubicin analogs prepared and described in this Thesis.

Chapter 2 describes successful and unsuccessful (semi-)synthetic routes towards *N,N*-dimethyldoxorubicin, with the aim of developing methodology towards more complex anthracyclines. The synthesis of 10 hybrid structures, filling the chemical space between monosaccharide doxorubicin and trisaccharide aclarubicin is described in **Chapter 3**, building on the use of Yu's gold(I) catalyzed glycosylation methodology to connect the glycans and anthraquinone aglycons. **Chapter 4** describes the design and synthesis of a set of doxorubicin analogs, varying in substituent or amine functionalization on the 3'-position of its sugar moiety. A series of regio- and stereoisomers of doxorubicin is described in **Chapter 5**. Finally, **Chapter 6** provides a summary of this Thesis, and describes prospects for future research.

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Chapter 2

Synthesis of N,N-*dimethyldoxorubicin*

Introduction

Since its discovery in the late 1960s, the anthracycline doxorubicin (**1a**, Figure 1) has fulfilled a crucial role in anti-cancer treatment.[1] Unfortunately, its clinical use comes with a range of side-effects, most notably cardiotoxicity,[2–4] which can be lethal and occurs in a dose-dependent manner. Treatment with doxorubicin is therefore limited by this cardiotoxicity to a maximum cumulative dose, and afterwards, many patients require alternate treatments, which are not always available. Additionally, doxorubicin-induced cardiac damage persists even after remission, severely lowering the quality of life of cancer survivors. Besides cardiotoxicity, doxorubicin is also able to induce the formation of secondary tumors[5,6] and infertility, especially troublesome in younger patients.[7] In spite of these side-effects that strongly hamper treatment, doxorubicin remains on the World Health Organisation's List of Essential Medicines.[8] Although liposomal administration of doxorubicin[9] resulted in lowered cardiotoxicity, the synthesis of analogs did not result in a less cardiotoxic anthracycline.[10] The recent discovery of histone eviction as a mode of action for this drug[11] brings renewed interest into the anthracycline class of anti-cancer drugs. In order to better understand the structure-activity relationship (SAR) of doxorubicin and analogs thereof, and ultimately yield a better anthracycline anti-cancer drug than doxorubicin, this Chapter presents the synthesis of *N,N*-dimethyldoxorubicin (**3**, Figure 1): a hybrid structure combining structural elements from both doxorubicin (**1a**) and aclarubicin (**2**).

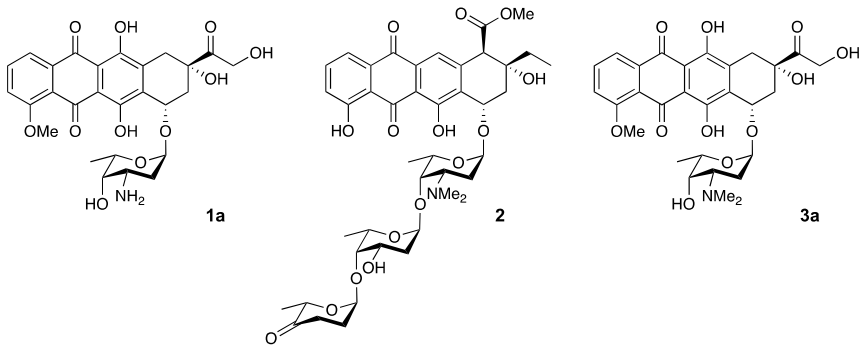
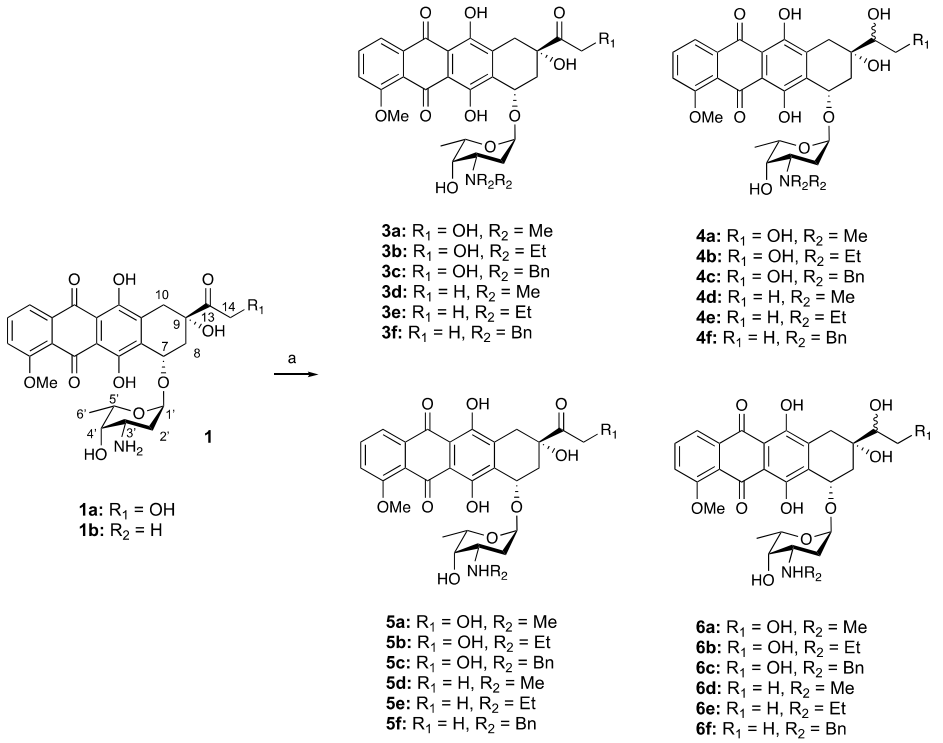


Figure 1. Doxorubicin (**1a**), aclarubicin (**2**) and the compound subject of this Chapter, *N,N*-dimethyldoxorubicin (**3a**).

Figure 1 shows the chemical structure of the cardiotoxic drug doxorubicin (**1a**), which has been shown to induce both DNA breaks and histone eviction.[11] Depicted as well is aclarubicin (**2**), a natural anthracycline that does not induce DNA damage, and is also less cardiotoxic in comparison to doxorubicin.[12] Considering the structures of these two drugs, a number of similarities and differences can be noted. Both compounds contain anthraquinone functions and share a general architecture, but they differ at places in substitution/oxidation pattern. Doxorubicin (**1a**) features an α-L-daunosamine as the single, monosaccharidic carbohydrate fragment. Aclarubicin features an α-L-rhodosamine (*N*,*N*-dimethyldaunosamine), that is further glycosylated on its 4-hydroxyl function with an α-(1→4) disaccharide composed of L-oliose and L-cinerulose A. Understanding of the structural basis of the difference in biological activities between doxorubicin (**1a**) and aclarubicin (**2**) would be greatly facilitated by the availability for evaluation of a series of hybrid structures of these two drugs. *N,N*-dimethyldoxorubicin (**3a**), combining the tetracycle present in doxorubicin and α-L-rhodosamine, the reducing sugar of aclarubicin (**2**) was envisaged as the first compound of such coherent set of hybrid anthracyclines.

N,N-dimethyldoxorubicin (**3a**), has been prepared previously by Tong *et al.*[13] They published a preparation that involves direct reductive alkylation of doxorubicin (**1a**) and daunorubicin (**1b**) to yield (di-)*N*-alkylated analogues **3a**-**3f** bearing two methyl, ethyl, and benzyl groups, respectively (Scheme 1). The yields were modest to low and were accompanied by unwanted reduction of the 13-(*bis*)-hydroxy ketone (**4a**-**4f**), mono-alkylated products (**5a**-**5f**) and compounds that had undergone both undesired transformations (**6a**-**6f**) in sometimes unspecified yields. Furthermore, the authors state that silica gel columns up to 7 feet (2.13 meters) were required to separate the products. They also found that the yields for reductive alkylation on daunorubicin (**1b**) (doxorubicin (**1a**) lacking the 14-OH group) were significantly higher.

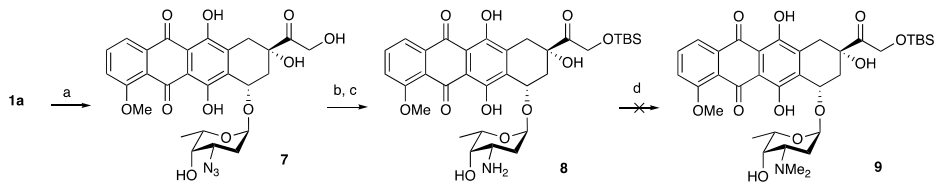


Scheme 1. Tong's synthesis of *N,N*-dimethyldoxorubicin (**3a**) and related dialkyl-doxorubicins and dialkyl-daunorubicins. *Reagents and conditions:* (a) aq. CH_2O, $NaBH_3CN$, MeCN, H_2O, 30 min, 43% for **3a**, 22% for **3b**, 3% for **3c**, 80% for **3d**, 37% for **3e**, 5% for **3f**.

Apparently, as also alluded to by the authors, the 13-*bis*-hydroxyketone moiety in doxorubicin (**1a**) is more susceptible to reduction than the hydroxyketone found in daunorubicin (**1b**). Borohydride reducing agents are known to reduce ketones when α-hydroxy substituents are present.[14,15] Attempts at reproducing the Tong method for the synthesis of *N,N*-dimethyldoxorubicin (**3a**) at the onset of the here-presented studies indeed led to extensive ketone reduction, incomplete amine alkylation, or both, and this synthesis route was therefore abandoned. The work described in this Chapter entails studies on the synthesis of *N,N*-dimethyldoxorubicin (**3a**), either by direct modification of doxorubicin (**1a**), or through glycosylation of the appropriately protected tetracycline aglycon with an orthogonally protected glycosyl donor using the gold(I)-glycosylation chemistry developed by the group of Yu.[16]

Results and discussion

One approach that would avoid ketone reduction as found in Tong's synthesis is shown in Scheme 2. In this strategy, the primary α-hydroxyl group that could direct the unwanted 13-ketone reduction is protected as its *tert*-butyldimethylsilyl ether (TBS). First, the amine in doxorubicin was protected as the azide by means of copper-catalyzed diazotransfer[17] to give **7**, following the procedure reported by Weil *et al*.[18] Subsequent regioselective silylation of the primary alcohol was followed by Staudinger reduction to give 14-*O*-TBS doxorubicin **8**. Reductive alkylation with formaldehyde using a sub-stoichiometric amount of sodium tris(acetoxy)borohydride ($NaBH(OAc)_3$), a milder reducing agent than $NaBH_3CN$, resulted in incomplete reductive alkylation and undesired ketone reduction. This might be a result of the intermediate methimine not being reactive enough towards borohydride reduction, due to hydrogen bonding with the 4'-hydroxyl group. As a result, the borohydride reduces the ketone instead.

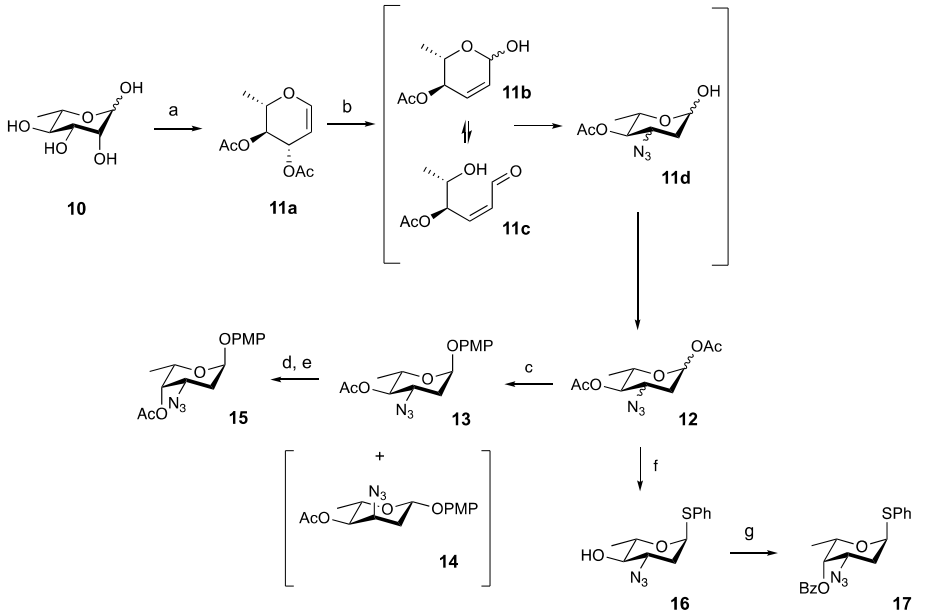


Scheme 2. Protection (steps a-c) of the 14-OH in doxorubicin (**1a**), in an attempt to prevent ketone reduction during reductive alkylation (step d). *Reagents and conditions:* (a) imidazole-1-sulfonyl azide hydrochloride, K_2CO_3, $CuSO_4 \cdot 5H_2O$, MeOH, 73%; (b) TBSCl, imidazole, DMF, 64%; (c) polymer-bound PPh_3, THF, H_2O, 50°C, 66%; (d) aq. CH_2O, $NaBH(OAc)_3$, EtOH.

The synthesis of *N,N*-dimethyldoxorubicin (**3a**) from an appropriately functionalized and protected donor glycoside and tetracycline aglycon was therefore investigated next. This strategy involves protecting both the 14- and the 4'-hydroxyl groups. Of note, such an approach should also allow for a larger variety of analogs to be prepared.

Since the discovery of doxorubicin (**1a**), a variety of strategies for the preparation of L-daunosaminyl donor glycosides has been published. Daunosamine can be obtained from acidic hydrolysis of doxorubicin itself, to yield daunosamine hydrochloride almost quantitatively.[19] Other methods for the preparation of daunosamine start from sugars (D-mannose[20], L-fucose[21], or L-rhamnose[21,22]) or even amino-acids (aspartic acid[23]). However, deriving large quantities of daunosamine from doxorubicin (€490 per gram[24]) was deemed too costly. Thus, preparation from either L-rhamnose or L-fucose was considered. L-fucose already possesses the correct stereochemistry on the 4-position, whereas L-rhamnose would require additional synthetic steps to invert this hydroxyl group. However, these additional steps are offset by the much lower cost of L-

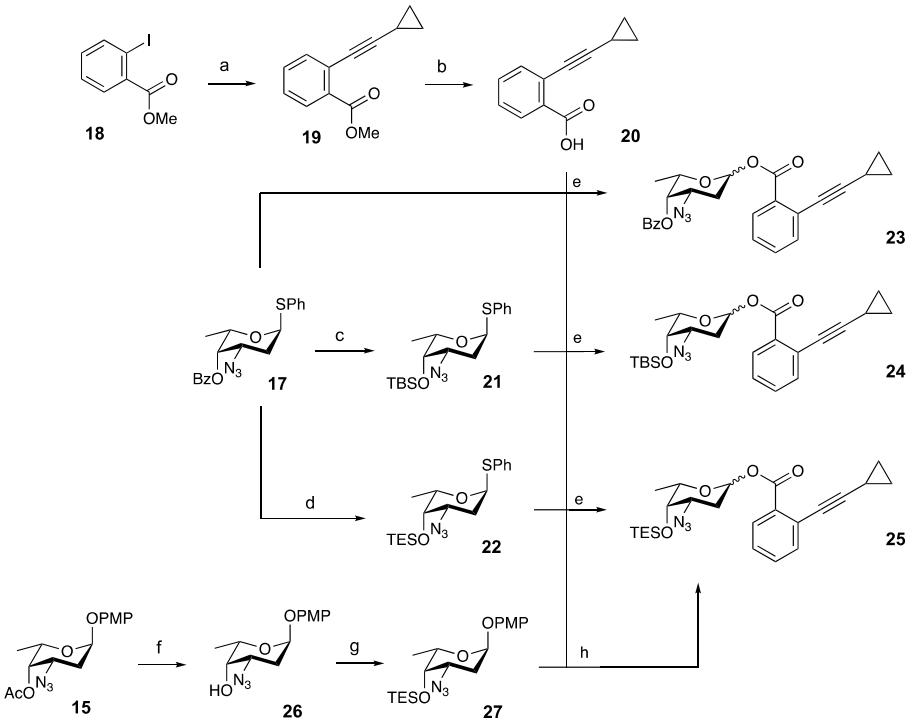
rhamnose (€275 per kg for L-rhamnose[25] versus $425 per 100 gram for L-fucose[26]) and also allowed for the preparation of daunosamine stereoisomers (see Chapter 5).



Scheme 2. Preparation of protected L-daunosamines **15** and **17**. *Reagents and conditions:* (a) *i.* Ac_2O, pyr.; *ii.* HBr/AcOH, Ac_2O, DCM; *iii.* Zn, AcOH, NaOAc, Ac_2O, $CuSO_4{\cdot}5H_2O$, MeCN, quant. over 3 steps; (b) *i.* H_2O, 80 °C, then NaN_3, AcOH; *ii.* Ac_2O, pyr., 83% over 2 steps; (c) *p*-methoxyphenol, TMSOTf, DCM, 0 °C, 50% of **13**, 10% of **14**, 83% total; (d) NaOMe, MeOH, 93%; (e) *i.* Tf_2O, pyr., DCM, 0 °C; *ii.* KOAc, 18-crown-6, DMF, 92% over 2 steps; (f) *i.* thiophenol, $BF_3{\cdot}OEt_2$, DCM, -78 to 0 °C; *ii.* NaOMe, MeOH, 39% over 2 steps; (g) *i.* Tf_2O, pyr., DCM, 0°C; *ii.* KOBz, 18-crown-6, DMF, 72% over 2 steps.

The synthesis of protected L-daunosamines **15** and **17** starting from L-rhamnose **10** commenced with the preparation of 3,4-di-*O*-acetyl-L-rhamnal **11a**.[27,28] To this end, L-rhamnose **10** was first peracetylated, then brominated at the anomeric position using HBr and finally subjected to a Zn/Cu-mediated elimination of the 1-bromide and 2-*O*-acetate in acetate buffer, to yield glycal **11a** in near quantitative yield over 3 steps. Heating this compound in water at 80 °C led to attack of water on the anomeric carbon to effect a shift of the 1,2-double bond to expel the acetate from C3 to give unsaturated alcohol **11b**. This alcohol is in equilibrium with 1,4-unsaturated aldehyde **11c**, which can undergo 1,4-addition of hydrazoic acid to give **12** as a mixture of 1- and 3- epimers, after anomeric acetylation. Treatment of this mixture with trimethysilyl trifluoromethanesulfonate (TMSOTf) in the presence of *p*-methoxyphenol afforded the corresponding anomeric *p*-methoxyphenyl acetals as a mixture of 1- and 3-epimers in 83% yield. From this, the desired α-configured C3-equatorial azide **13** could be separated in 50% overall yield (kedarosamine **14** was also isolated in 10% and used in

syntheses described in Chapter 5). Deacetylation, triflation and inversion[29] then gave **15**. In a similar vein, subjection of mixture **12** to $BF_3{\cdot}OEt_2$ and thiophenol followed by 4-deacetylation gave **16**. Triflation of the resultant equatorial alcohol was followed by S_N2-inversion of stereochemistry with potassium benzoate to finally give orthogonally protected **17**.

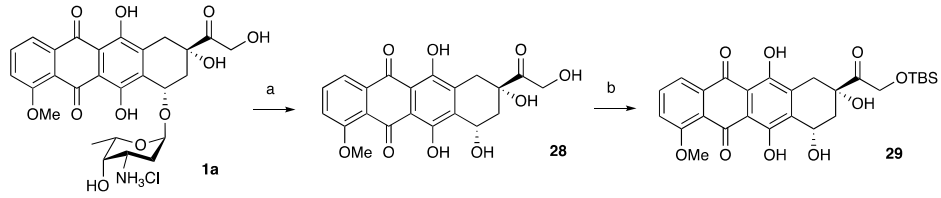


Scheme 3. Preparation of the L-daunosaminyl *ortho*-alkynylbenzoate donors **23**-**25**. *Reagents and conditions:* (a) cyclopropylacetylene, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, 96%; (b) aq. NaOH, THF; (c) *i*. aq. NaOH, dioxane, MeOH, 60°C; *ii. tert*-butyldimethylsilyl triflate, pyr., DMF, 83% over 2 steps; (d) *i*. aq. NaOH, dioxane, MeOH, 60°C; *ii.* triethylsilyl triflate, pyr., DMF, 95% over 2 steps; (e) *i. N*-iodosuccinimide, MeCN/H_2O (10:1, v/v); *ii.* EDCI·HCl, DIPEA, DMAP, DCM, 68% for **23,** 43% for **24**, 20% for **25**, over 2 steps; (f) NaOMe, MeOH, 93%; (g) triethylsilyl triflate, pyr., DMF, quant.; (h) *i.* Ag(II)(hydrogen dipicolinate)$_2$, NaOAc, MeCN, H_2O, 0 °C; *ii.* EDCI·HCl, DIPEA, DMAP, DCM, 75% over 2 steps (1:5.6 α:β).

Protected L-daunosaminyl thioglycoside **17** was then converted to its corresponding 4-silyl ether. Hydrolysis of the benzoate was followed by either *tert*-butyldimethylsilylation or triethylsilylation. The 4-hydroxyl function appeared unreactive towards silyl chlorides, even at elevated temperatures. Use of the corresponding silyl triflates afforded **21** and **22** in good yields. In order to convert these thioglycosides into their corresponding *ortho*-alkynylbenzoates, *ortho*-cyclopropylethynylbenzoic acid **20**[30] was prepared. According to the literature procedure,[31] methyl-2-iodobenzoate **18** was subjected to Sonogashira conditions

($Pd(PPh_3)_2Cl_2$, CuI, Et_3N) in the presence of cyclopropylacetylene to yield *ortho*-alkynylbenzoate methyl ester **19**. The carboxylic acid was then liberated by means of aqueous hydrolysis to give **20**. However, this acid proved to be particularly unstable, and undergoes intramolecular cyclisation to afford the corresponding *iso*-coumarins. This reagent was therefore best prepared fresh (by means of saponification) and used in excess in its Steglich esterification. Then, thioglycosides **17**, **21** and **22** were subjected to hydrolysis (*N*-iodosuccinimide in wet MeCN) to yield their corresponding hemiacetals. Steglich esterification of these with carboxylic acid **20** yielded the three different alkynylbenzoate donors. In this way, the α- and β-benzoates **23α** and **23β** (separated by column chromatography) were obtained in good yield over the two steps. Treatment of silyl ethers **21** and **22** led to extensive cleavage of the silyl protecting groups (giving **24** and **25** in 43% and 20% respectively, over two steps), presumably due to *in situ* generated molecular iodine, which is known to cleave silyl ethers in a catalytic fashion.[32] In an attempt to improve the yield of **25**, *p*-methoxyphenolate **15** was converted to its 4-*O*-triethylsilylether. Removal of the anomeric *p*-methoxyphenolate was achieved using the single-electron oxidant silver(II)-di(hydrogen picolinate) ($Ag(DPAH)_2$),[33,34] a reagent that was able to oxidize the *p*-methoxyphenolate into 1,4-benzoquinone under buffered conditions, thereby releasing the desired lactol. Ensuing esterification now gave alkynylbenzoate **25** in 75% over two steps. The glycosyl donors **23-25** were obtained as anomeric mixtures (with the β-product predominating). Because anomeric 2-deoxy *ortho*-alkynylbenzoates can interconvert under glycosylation conditions[35] and both anomers behave equally well in glycosylations,[31] this was expected to be of little influence on the outcome of the projected glycosylations.

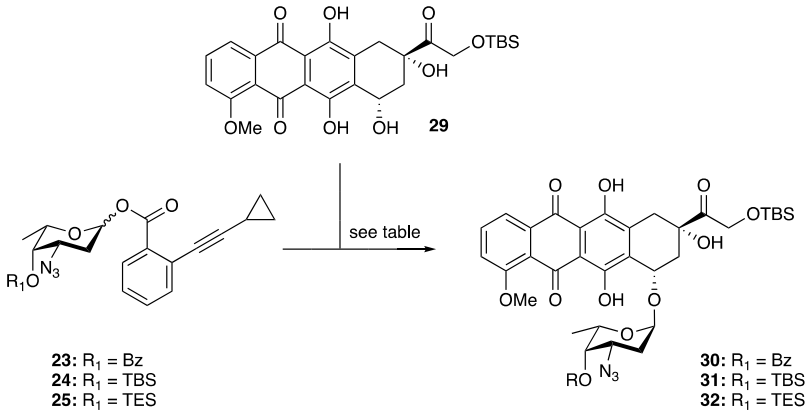
Attention was then turned to the synthesis of protected doxorubicinone aglycone acceptor **29**. Doxorubicinone (**28**) has been prepared by (lengthy) total synthesis[36–38] and formally from daunomycinone[39] but is more easily obtained by acidic hydrolysis of the glycosidic linkage in doxorubicin (**1a**), as shown in Scheme 4. This was followed by regioselective silylation of the primary alcohol to give acceptor **29** in near quantitative yield over the two steps.[40]



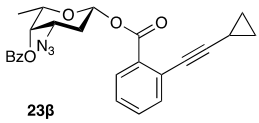
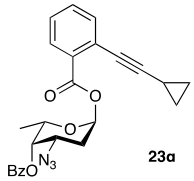
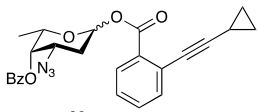
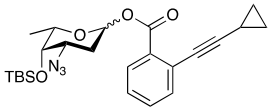
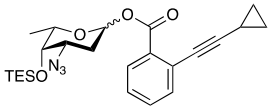
Scheme 4. Synthesis of doxorubicinone-acceptor **29**. *Reagents and conditions:* (a) *i.* aq. HCl, 90 °C; (b) TBS-Cl, imidazole, DMF, 97% over 2 steps.

Having both glycosylation partners in hand, their behavior in PPh_3AuNTf_2-mediated glycosylations was investigated. The results are summarized in Table 1.

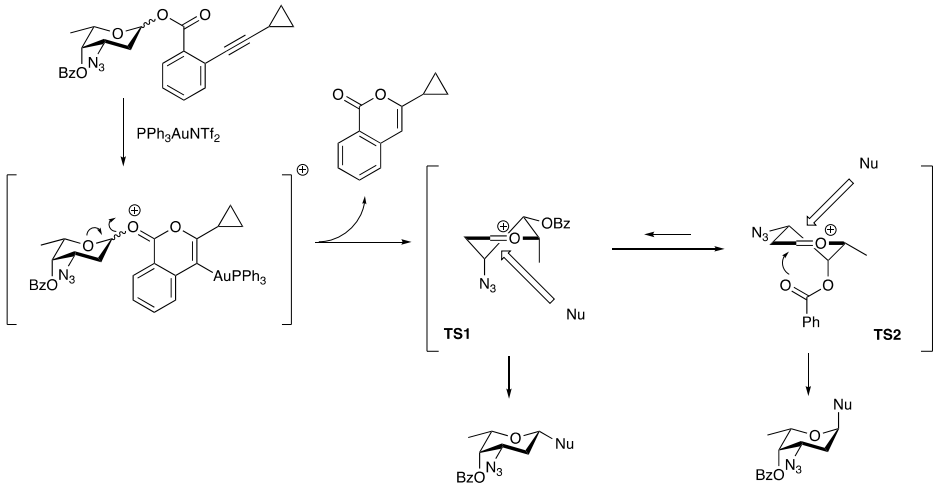
Table 1. Glycosylation of *ortho*-alkynylbenzoates **23**-**25** to doxorubicinone-acceptor **29**.



Reagents and conditions: (a) PPh_3AuNTf_2 (10 mol%), 4Å MS, T, 0.05M in DCM.

Entry	Donor	Temperature	Acceptor **29** equiv.	Yield (α:β ratio)
1	 **23β**	-78 °C to RT	1	25% (>20:1 α:β)
2	 **23α**	-78 °C to RT	1	25% (>20:1 α:β)
3	 **23**	RT	1	71% (>20:1 α:β)
4	 **24**	RT	1.5	78% (>20:1 α:β)
5	 **25**	RT	1.5	73% (>20:1 α:β)

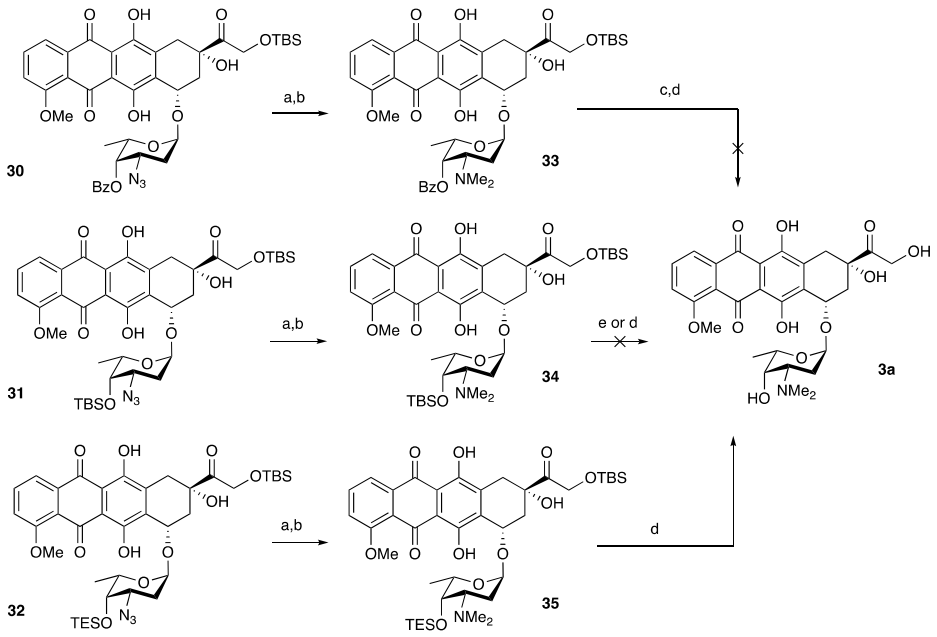
From entries 1 and 2 it appears that the anomeric stereochemistry of the prepared glycosyl donors is of little influence, as they performed equally well in the glycosylation reactions. Addition of a catalytic amount of PPh_3AuNTf_2 to a mixture of either donor **23α** or **23β** and acceptor **29** at -78 °C was followed by gradual warming up to RT to give **30** with excellent α-selectively in both cases. A rationale for the stereochemical outcome is shown in Scheme 5.



Scheme 5. Mechanistic rationale for the observed stereoselectivity of the glycosylation to donor **19**.

Association of the gold(I) catalyst to the triple bond in the anomeric alkynylbenzoate is followed by attack of the carbonyl onto the alkyne to yield an isochromenylium-gold complex, which can collapse to give an oxocarbenium-like intermediate. This species may adopt different conformations, of which the $^4H_3$ (TS1) and $^3H_4$ (TS2) are likely the most stable. Although the $^3H_4$-conformer places the large benzoate in a sterically unfavoured axial position, it may benefit from long-range anchimeric stabilization. Top-face attack on this species, provides the α-anomeric product, through a favorable chair-like transition state. Conversely, in the $^4H_3$ conformer, attack of the incoming nucleophile on the bottom face of the half-chair to allow for a chair like transition state, would lead to significant steric hindrance when passing the axial methyl and azide groups. The low yield of the reactions depicted in entries 1 and 2 is likely due to the observed poor solubility of the anthracycline acceptor in the reaction solvent at low temperature. Performing the same reaction at RT almost tripled the yield. At this temperature, the reaction was complete within 10 minutes, with the initial red suspension turning into a clear red liquid in mere seconds, maintaining the stereoselectivity of the reaction.

Donor glycosides featuring either a triethyl- or a *tert*-butyldimethylsilyl ether (Entries 4 and 5) gave excellent stereoselectivity upon glycosylation to give **31** and **32**. The oxocarbenium ion-like intermediates derived from these donors, likely prefer to adopt a $^3H_4$ conformation, which are selectively attacked on the α-face. In these reactions the amount of acceptor **29** was increased, to decrease the possibility of additional glycosylation onto the tertiary alcohol, a side-reaction observed in the usage of excess donor.[41] Excess acceptor **29** could be easily recovered through silica gel column chromatography of the glycosylation reaction mixtures.



Scheme 6. Final steps towards *N,N*-dimethyldoxorubicin (**3a**). *Reagents and conditions:* (a) polymer-bound PPh_3, THF/H_2O (10:1, v/v), 50 °C, 48% from **30**, 75% from **31**, 69% from **32**; (b) aq. CH_2O, $NaBH(OAc)_3$, EtOH, 53% for **33**, 45% for **34**, 83% for **35**; (c) MeOH, reflux; (d) HF·pyr., THF/pyr., 66% from **35**; (e) TBAF, THF.

For all three obtained glycosidic products **30**-**32**, Staudinger reduction of the azide gave the corresponding free amines (Scheme 6). Subsequent *N*-dimethylation was achieved using a sub-stoichiometric amount of sodium tris(acetoxy)borohydride in the presence of aqueous formaldehyde to effect reductive alkylation and yield **33**-**35**. In contrast to the preparation of **9** (Scheme 2), little to no ketone reduction was observed here. Apparently, hydrogen bonding of the 4'-hydroxyl with the intermediate methimine is abolished upon protection of this function with either a benzoate or silyl ether. The final deprotections proved less facile, with attempts at removal of the benzoyl group in **33** (MeOH, reflux[42]) leading to degradation. The 4-OTBS group in **34** also proved to be

troublesome, with TBAF treatment giving a complex mixture and HF·pyridine unable to remove the 4-OTBS group, even after a prolonged reaction time (7 days). However, the TES group in **35** could be readily removed by treatment with HF·pyridine, to give the target *N,N*-dimethyldoxorubicin (**3a**) in 66% yield.

Conclusions

This Chapter describes the synthesis of *N,N*-dimethyldoxorubicin (**3a**), a hybrid structure combining structural elements from both doxorubicin (**1a**) and aclarubicin (**2**). As direct reductive alkylation on the natural drug proved troublesome, protected doxorubicin was prepared from carefully chosen glycosyl donors and acceptors. Gold(I) catalysis was able to promote the glycosylations, delivering the target compounds in good yields and excellent α-stereoselectivity. The final removal of the 4'-protecting group proved difficult but the use of the triethylsilyl group, which could be removed under mild conditions, allowed for the preparation of *N,N*-dimethyldoxorubicin (**3a**). The glycosylation methodology and protecting group strategy applied in this Chapter is further explored in the synthesis of doxorubicin/aclarubicin hybrid structures as described in Chapter 3.

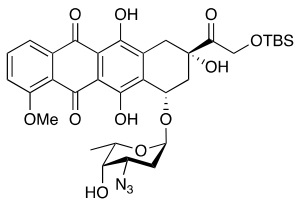
Experimental procedures and characterization data

All reagents were of commercial grade and used as received. Traces of water from reagents were removed by co-evaporation with toluene in reactions that required anhydrous conditions. All moisture/oxygen sensitive reactions were performed under an argon atmosphere. DCM used in the glycosylation reactions was dried with flamed 4Å molecular sieves before being used. Reactions were monitored by TLC analysis with detection by UV (254 nm) and where applicable by spraying with 20% sulfuric acid in EtOH or with a solution of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4\cdot 2H_2O$ (10 g/L) in 10% sulfuric acid (aq.) followed by charring at ~150 °C. Flash column chromatography was performed on silica gel (40-63μm). ^1H and ^{13}C spectra were recorded on a Bruker AV 400 and Bruker AV 500 in $CDCl_3$, CD_3OD, pyridine-d5 or D_2O. Chemical shifts (δ) are given in ppm relative to tetramethylsilane (TMS) as internal standard (^1H NMR in $CDCl_3$) or the residual signal of the deuterated solvent. Coupling constants (J) are given in Hz. All ^{13}C spectra are proton decoupled. Column chromatography was carried out using silica gel (0.040-0.063 mm). Size-exclusion chromatography was carried out using Sephadex LH-20, using DCM:MeOH (1:1, v/v) as the eluent. Neutral silica was prepared by stirring regular silica gel in aqueous ammonia, followed by filtration, washing with water and heating at 150°C overnight. High-resolution mass spectrometry (HRMS) analysis was performed with a LTQ Orbitrap mass spectrometer (Thermo Finnigan), equipped with an electronspray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10 mL/min, capillary temperature 250 °C) with resolution R = 60000 at m/z 400 (mass range m/z = 150 – 2000) and dioctyl phthalate (m/z = 391.28428) as a "lock mass", or with a Synapt G2-Si (Waters), equipped with an electronspray ion source in positive mode (ESI-TOF), injection via NanoEquity system (Waters), with LeuEnk (m/z = 556.2771) as "lock mass". Eluents used: MeCN:H_2O (1:1 v/v) supplemented with 0.1% formic acid. The high-resolution mass spectrometers were calibrated prior to measurements with a calibration mixture (Thermo Finnigan).

General procedure A: Au(I)-catalysed glycosylation

To a solution of the glycosyl donor (1 eq) and the required anthracycline acceptor (1-1.5 eq) in DCM (0.05M), activated molecular sieves (4Å) were added. The mixture was stirred for 30 minutes. Subsequently, a freshly prepared 0.1M DCM solution of PPh_3AuNTf_2 (prepared by stirring 1:1 PPh_3AuCl and $AgNTf_2$ in DCM for 30 minutes) (0.1 eq) in DCM was added dropwise at the designated temperature. After stirring 30 minutes (for RT) or overnight (-20°C or lower), the mixture was filtered and concentrated *in vacuo*. Column chromatography (EtOAc:pentane or Et_2O:pentane and then acetone:toluene) followed by (if required) size-exclusion chromatography (Sephadex LH-20, DCM/MeOH, 1:1 v/v) gave the title compounds.

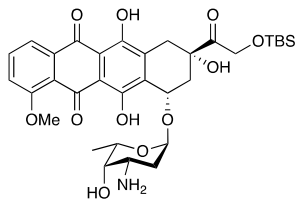
7-[3-Azido-2,3-dideoxy-L-fucopyranoside]-14-O-tert-butyldimethylsilyl-doxorubicinone (7)



To a mixture of doxorubicin hydrochloride (**1a**) (200 mg, 0.340 mmol), potassium carbonate (72 mg, 0.51 mmol, 1.5 eq) and copper sulfate (cat. amount) in methanol (4 mL) was added imidazole-1-sulfonyl azide hydrochloride[17] (22 mg, 0.1035 mmol, 3.3 eq) and the reaction mixture was stirred overnight. The mixture diluted with water and extracted with DCM thrice. The combined organic layers dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography (10:90 MeOH:DCM) gave 3'-azidodoxorubicin as a red solid (140 mg, 0.248 mmol, 72%). Spectral data was in accordance with that of literary precedence.[43] To a solution of the above azide (126 mg, 0.221 mmol) in DMF (4.4 mL) were added imidazole (38 mg, 0.55 mmol) and then *tert*-butyldimethylsilyl chloride (50 wt% in toluene, 85 μL, 1.1 eq) at 0°C and the resulting mixture was stirred for 3 days. Then, equal such portions of both imidazole and *tert*-butyldimethylsilyl chloride were added at 0°C and the mixture was stirred overnight. A third portion was added, and after 3 hours of stirring, the reaction mixture was poured into Et_2O and washed with H_2O thrice. The organic layer was then diluted with DCM, dried over Na_2SO_4 and concentrated *in vacuo* (the use of $MgSO_4$ for the drying of doxorubicinone-containing compounds led to extensive degradation). Column chromatography (2:98 – 20:80 acetone:toluene) gave the title compound as a red solid (90 mg, 0.13 mmol, 64%). ^1H NMR (400 MHz, Chloroform-*d*) δ 13.87 (s, 1H), 13.05 (s, 1H), 7.92 (d, *J* = 7.6 Hz, 1H), 7.74 (t, *J* = 8.1 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 5.54 (d, *J* = 3.7 Hz, 1H), 5.18 (dd, *J* = 4.1, 2.0 Hz, 1H), 4.87 (d, *J* = 2.8 Hz, 2H), 4.35 (s, 1H), 4.07 (s, 5H), 3.74 (s, 1H), 3.60 (ddd, *J* = 12.8,

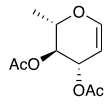
4.9, 2.4 Hz, 1H), 3.09 (dd, *J* = 18.6, 1.8 Hz, 1H), 2.76 (d, *J* = 18.8 Hz, 1H), 2.30 (d, *J* = 14.7 Hz, 2H), 2.14 (ddd, *J* = 29.8, 13.9, 4.0 Hz, 2H), 1.94 (dd, *J* = 13.2, 4.9 Hz, 1H), 1.33 (d, *J* = 6.5 Hz, 3H), 0.97 (s, 9H), 0.15 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.0, 186.7, 186.4, 161.0, 156.2, 155.5, 135.8, 135.2, 133.8, 133.6, 120.5, 119.8, 118.6, 111.3, 111.2, 100.8, 70.3, 69.5, 67.2, 66.7, 56.7, 56.7, 35.5, 33.7, 28.5, 25.9, 18.7, 16.9, -5.2. HRMS: $[M + Na]^+$: calculated for $C_{33}H_{41}N_3O_{11}SiNa$: 706.2408; found 706.2401.

7-[3-Amino-2,3-dideoxy-L-fucopyranoside]-14-O-tert-butyldimethylsilyl-doxorubicinone (8)



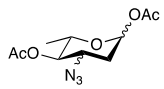
A suspension of **7** (200 mg, 0.292 mmol) and polymer-bound triphenylphosphine (490 mg, 1.46 mmol, 5 eq) in THF/H_2O (22 mL, 10:1 v/v) was stirred at 50°C overnight. It was then filtered off and concentrated *in vacuo*. Column chromatography (5:95 – 20:80 MeOH:DCM) gave the title compound as a red solid (127 mg, 0.193 mmol, 66%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.71 (s, 2H), 7.42 (d, *J* = 7.6 Hz, 1H), 5.37 (s, 1H), 4.23 (q, *J* = 6.4 Hz, 1H), 3.96 (s, 3H), 3.62 (s, 1H), 3.38 (d, *J* = 11.6 Hz, 1H), 2.95 (d, *J* = 18.5 Hz, 1H), 2.74 (d, *J* = 18.5 Hz, 1H), 2.28 (d, *J* = 14.6 Hz, 1H), 2.13 – 2.00 (m, 1H), 2.00 – 1.80 (m, 2H), 1.29 (d, *J* = 6.4 Hz, 3H), 0.97 (s, 9H), 0.14 (d, *J* = 3.3 Hz, 6H). ^{13}C NMR (101 MHz, MeOD) δ 213.3, 162.3, 157.2, 137.2, 136.1, 135.4, 121.2, 120.4, 120.2, 112.2, 112.0, 112.0, 101.7, 77.3, 71.4, 69.2, 68.2, 67.3, 57.1, 48.2, 40.3, 37.2, 33.8, 30.9, 26.4, 19.5, 17.3, -5.1.

3,4-Di-*O*-acetyl-L-rhamnal (11)



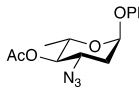
Commercially available L-rhamnose monohydrate **10** (20.0 g, 110.0 mmol) was suspended in pyridine (100 mL) and acetic anhydride (128 mL). After stirring for three days, the resulting solution was concentrated *in vacuo* and additionally coevaporated with toluene to afford crude per-*O*-acetyl-L-rhamnose as a viscous orange oil. The material was carried on without further purification. This tetraacetate was dissolved in DCM (70 mL) and acetic anhydride (3.6 mL), whereupon hydrobromic acid (33 wt. % HBr in AcOH, 33 mL) was added dropwise. After stirring for 3 hours, the resulting solution was concentrated *in vacuo* to afford the crude rhamnosyl bromide as a viscous green oil. The material was continued without further purification. To a stirring suspension of copper sulfate pentahydrate (3.50 g, 22.0 mmol, 0.2 eq), sodium acetate (16.2 g, 198.0 mmol, 1.8 eq), acetic acid (12.6 mL, 220.0 mmol, 2 eq) and acetic anhydride (14.5 mL, 154.0 mmol, 1.4 eq), in MeCN (50 mL) was added zinc dust (14.4 g, 220.0 mmol, 2 eq) and the resulting suspension was stirred for 45 minutes. Subsequently, a solution of the rhamnosyl bromide in MeCN (250 mL) was added *via* a dripping funnel over the duration of 40 minutes to the mixture of activated zinc. After stirring for 2 hours, the resulting suspension was diluted with DCM, filtered over Celite and successively washed with sat. aq. $NaHCO_3$. The aqueous layer was then extracted with DCM and the resulting combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound as a light-yellow oil (23.6 g, 110.0 mmol, 100% over 3 steps). Spectral data was in accordance with that of literary precedence.[28]

***p*-Methoxyphenyl-4-O-acetyl-3-azido-2,3-dideoxy-L-rhamno/fucopyranoside (12)**[22]



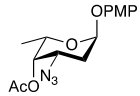
Glycal **11** (25.9 g, 121 mmol) in was emulsified in H_2O (170 mL) and heated at 80°C for 2 h. After cooling to room temperature, acetic acid (25.2 mL) and NaN_3 (10.9 g, 297 mmol, 1.4 eq) were added and the reaction mixture was stirred overnight. Sat. aq. $NaHCO_3$ was added and the reaction mixture was extracted thrice with EtOAc. Combined organics were dried over $MgSO_4$ and concentrated in vacuo. To the crude product in DCM (210 mL) were added pyridine (60 mL) and acetic anhydride (60 mL) and the reaction mixture was stirred overnight. It was then concentrated *in vacuo* and partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to afford **8** as an orange oil. (25.4 g, 98.9 mmol, 82% over 2 steps).

***p*-Methoxyphenyl-4-O-acetyl-3-azido-2,3-dideoxy-α-L-rhamnopyranoside (13)**



12 (11.6 g, 45.0 mmol) and *p*-methoxyphenol (8.38 g, 67.5 mmol, 1.5 eq) were coevaporated thrice with toluene and subsequently dissolved in DCM (225 mL). Activated 4Å molecular sieves were added, and the mixture was allowed to stir for 30 minutes. Thereafter, TMSOTf (2.44 mL, 13.5 mmol, 0.3 eq) was added at 0°C and the mixture was stirred for a further 4 hours at that temperature. It was then filtered into sat. aq. $NaHCO_3$, after which the organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (7:93 EtOAc:pentane) gave the title compound as a white solid (7.20 g, 22.4 mmol, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 – 6.92 (m, 2H), 6.92 – 6.78 (m, 2H), 5.47 (d, *J* = 2.7 Hz, 1H), 4.75 (t, *J* = 9.8 Hz, 1H), 4.07 (ddd, *J* = 12.3, 9.9, 5.0 Hz, 1H), 3.93 (dq, *J* = 9.8, 6.3 Hz, 1H), 3.77 (s, 3H), 2.36 (ddd, *J* = 13.3, 4.9, 1.1 Hz, 1H), 2.14 (s, 3H), 1.86 (td, *J* = 12.9, 3.5 Hz, 1H), 1.13 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 155.0, 150.4, 117.6, 114.7, 95.5, 76.8, 75.5, 66.7, 57.6, 55.7, 35.5, 20.9, 17.6. HRMS: $[M + Na]^+$: calculated for $C_{15}H_{19}N_3O_5Na$: 344.1217; found 344.1233.

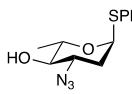
***p*-Methoxyphenyl-4-O-acetyl-3-azido-2,3-dideoxy-α-L-fucopyranoside (15)**



To a solution of **13** (7.20 g, 22.4 mmol) in MeOH was added NaOMe (242 mg, 4.48 mmol, 0.2 eq) and the mixture was allowed to stir over 3 days. It was then neutralized by addition of Amberlite IR120 (H^+ form), filtered off and concentrated *in vacuo* to give the alcohol as a yellow oil (6.26 g, 22.4 mmol, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 – 6.94 (m, 2H), 6.88 – 6.79 (m, 2H), 5.47 (d, *J* = 2.8 Hz, 1H), 3.96 (ddd, *J* = 12.2, 9.5, 4.9 Hz, 1H), 3.83 (dq, *J* = 9.3, 6.2 Hz, 1H), 3.78 (s, 3H), 3.22 (td, *J* = 9.4, 4.1 Hz, 1H), 2.36 (ddd, *J* = 13.2, 4.9, 1.1 Hz, 1H), 2.26 (d, *J* = 4.2 Hz, 1H), 1.85 (td, *J* = 12.7, 3.5 Hz, 1H), 1.26 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.0, 150.6, 117.7, 114.7, 95.8, 76.8, 76.1, 68.5, 60.4, 55.8, 35.3, 17.9. HRMS: $[M+Na]^+$ calculated for $C_{13}H_{17}N_3O_4$; 302.1111; found 302.1118.

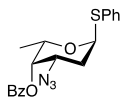
To a solution of the above compound (18.09 g, 64.8 mmol) in DCM (250 mL) and pyridine (25 mL), triflic anhydride (13.5 mL, 77.8 mmol, 1.2 eq) was added at 0°C. The mixture was allowed to stir for 1 hour, after which it was poured into 1M HCl solution. This was then extracted with DCM twice, the organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting crude triflate and 18-crown-6 (20.5 g, 77.8 mmol, 1.2 eq) were coevaporated thrice with toluene and dissolved in DMF (250 mL). To this was added KOAc (7.6 g, 77.8 mmol, 1.2 eq) and the mixture was stirred for 1 hour. It was then diluted with EtOAc and washed with H_2O five times and brine. The organic layer was then dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (5:95 - 7:93 EtOAc:pentane) gave the title compound as a yellow solid (19.2 g, 59.8 mmol, 92% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 – 6.91 (m, 2H), 6.91 – 6.75 (m, 2H), 5.60 (d, *J* = 2.4 Hz, 1H), 5.22 (d, *J* = 2.5 Hz, 1H), 4.14 (q, *J* = 6.2 Hz, 1H), 4.05 (ddd, *J* = 12.3, 5.1, 3.0 Hz, 1H), 3.78 (s, 3H), 2.28 – 2.07 (m, 2H), 1.11 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 155.0, 150.7, 117.6, 114.8, 96.3, 76.8, 70.2, 66.0, 55.8, 54.6, 29.9, 20.9, 16.8. HRMS: $[M + Na]^+$ calculated for $C_{15}H_{19}N_3O_5Na$: 344.1217; found 344.1233.

Phenylthio-3-azido-4-*O*-benzoyl-2,3-dideoxy-α-L-rhamnopyranoside (16)[44]



A solution of **12** (12.9 g, 50.0 mmol) in DCM (250 mL) was cooled to -78 °C, after which thiophenol (5.25 mL, 51.5 mmol, 1.03 eq) and $BF_3{\cdot}OEt_2$ (15.4 mL, 125 mmol, 2.5 eq) were added dropwise. After being allowed to warm up to 0 °C, the reaction mixture was poured into sat. aq. $NaHCO_3$, extracted with DCM thrice, dried over $MgSO_4$ and concentrated *in vacuo*. This crude product was then dissolved in MeOH (500 mL), after which methanolic NaOMe (5.4 M in MeOH) was added until pH>10. It was then quenched by addition of Amberlite (H^+ form), filtered and the filtrate was concentrated *in vacuo*. Column chromatography (4:96 – 5:95 EtOAc:pentane) gave the title compound as a clear oil (5.17 g, 19.5 mmol, 39% over 2 steps). Spectral data was in accordance with that of literary precedence.

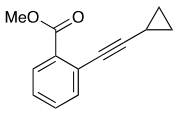
Phenylthio-3-azido-4-*O*-benzoyl-2,3-dideoxy-α-L-fucopyranoside (17)



To a solution of **16** (5.17 g, 19.5 mmol) in DCM (80 mL) and pyridine (8 mL), triflic anhydride (4.1 mL, 23.4 mmol, 1.2 eq) was added at 0°C. The mixture was allowed to stir for 1 hour, after which it was poured into 1M HCl solution. This was then extracted with DCM twice, the organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting crude triflate and 18-crown-6 (7.21 g, 27.3 mmol, 1.4 eq) were coevaporated thrice with toluene and dissolved in DMF (75 mL). To this was added potassium benzoate (4.37 g, 27.3 mmol, 1.2 eq) and the mixture was stirred for 1.5 hours. It was then diluted with EtOAc and washed with H_2O five times and brine. The organic layer was then dried over $MgSO_4$

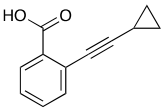
and concentrated *in vacuo*. Column chromatography (4:90 - 10:90 Et_2O:pentane) gave the title compound as a yellow oil (5.27 g, 14.3 mmol, 72% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.18 – 8.04 (m, 2H), 7.67 – 7.54 (m, 1H), 7.54 – 7.39 (m, 4H), 7.39 – 7.20 (m, 3H), 5.81 (d, *J* = 5.5 Hz, 1H), 5.60 – 5.39 (m, 1H), 4.59 (qd, *J* = 6.5, 1.3 Hz, 1H), 4.02 (ddd, *J* = 12.9, 4.7, 3.0 Hz, 1H), 2.57 (td, *J* = 13.2, 5.7 Hz, 1H), 2.21 (ddt, *J* = 13.3, 4.7, 1.2 Hz, 1H), 1.19 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 134.3, 133.5, 131.4, 130.0, 129.4, 129.1, 128.6, 127.5, 83.7, 70.4, 66.4, 56.0, 30.8, 16.8. HRMS: $[M + Na]^+$ calculated for $C_{19}H_{19}N_3O_3SNa$: 392.1045; found 392.1043.

Methyl *ortho*-cyclopropylethynylbenzoate (19)[31]



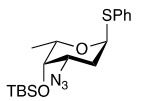
A flame dried flask was charged with methyl 2-iodobenzoate **18** (49.1 g, 200 mmol) and Et_3N (300 mL). The solution was degassed by sonication and cooled to 0°C. $Pd(PPh_3)_2Cl_2$ (2.81 g, 4.00 mmol, 0.02 eq) and CuI (762 mg, 4.00 mmol, 0.02 eq) were added. Cyclopropylacetylene (22.7 ml, 2.60 mmol, 1.3 eq) was then added dropwise at the same temperature. The reaction mixture was allowed to warm to room temperature and stirred overnight. 500 mL sat aq. NH_4Cl was added, stirred vigorously for 30 min and extracted pentane (600 mL) and EtOAc in pentane (600 mL, 1:99 v/v). Combined organics were washed with H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo.* Column chromatography (3:97 – 10:90 Et_2O:pentane) afforded the title compound as a pale-yellow oil (38.05 g, 192.3 mmol, 96%). Spectral data was in accordance with that of literary precedence.[45]

***ortho*-Cyclopropylethynylbenzoic acid (20)**



A solution of **19** in THF (5 mL/mmol) and 1M NaOH (5 mL/mmol) was stirred at 50°C for 8 hours. It was then poured into 1M HCl (6 mL/mmol) and extracted with DCM 3x. The combined organic layers were then dried over $MgSO_4$ and concentrated *in vacuo*. The title acid thus obtained was used without further purification, due to its instability. Spectral data of the purified compound was in accordance with that of literary precedence.[45]

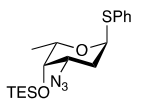
Phenylthio-3-azido-4-*O*-*tert*-butyldimethylsilyl-2,3-dideoxy-α-L-fucopyranoside (21)



A solution of **17** (753 mg, 2.04 mmol) in 1M NaOH (45 mL), dioxane (40 mL) and MeOH (40 mL) was stirred at 60 °C for 1 hour. It was then concentrated *in vacuo* and partitioned between EtOAc and aq. sat. NH_4Cl. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give the crude alcohol.

This was then redissolved in DMF (3.4 mL) to which pyridine (342 µL, 4.25 mmol) and TBSOTf (370 µL, 2.04 mmol) were added at 0°C. After stirring overnight, additional such portions of pyridine and TBSOTf were added at the same temperature and again stirred overnight. The reaction mixture was then diluted with EtOAc, washed with H_2O five times, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (5:95 Et_2O:pentane) gave the title compound as a clear oil (537 mg, 1.41 mmol, 69% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.62 – 7.38 (m, 2H), 7.38 – 7.16 (m, 3H), 5.68 (dd, *J* = 5.6, 1.3 Hz, 1H), 4.43 – 4.17 (m, 1H), 3.81 (ddd, *J* = 12.6, 4.2, 2.5 Hz, 1H), 3.73 – 3.61 (m, 1H), 2.53 (td, *J* = 12.8, 5.5 Hz, 1H), 2.00 (ddt, *J* = 12.9, 4.2, 1.2 Hz, 1H), 1.18 (d, *J* = 6.5 Hz, 3H), 0.94 (s, 9H), 0.18 (s, 3H), 0.10 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.8, 131.5, 129.1, 127.3, 83.8, 70.7, 68.2, 58.5, 29.7, 26.1, 18.5, 17.7, -4.0, -4.3. HRMS: $[M + H]^+$ calculated for $C_{18}H_{30}N_3O_2Si$: 380.1828; found 380.1823.

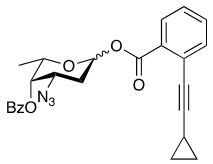
Phenylthio-3-azido-4-*O*-triethylsilyl-2,3-dideoxy-α-L-fucopyranoside (22)



A solution of **17** (810 mg, 2.19 mmol) in 1M NaOH (50 mL), dioxane (45 mL) and MeOH (45 mL) was stirred at 60°C for 1 hour. It was then concentrated *in vacuo* and partitioned between EtOAc and aq. sat. NH_4Cl. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo* to give the crude alcohol.

This was then redissolved in DMF (3.7 mL) to which pyridine (529 µL, 6.57 mmol, 3 eq) and TESOTf (891 µL, 3.94 mmol) were added at 0°C. After stirring for 1 hour, the reaction mixture was then diluted with EtOAc, washed with H_2O five times, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (5:95 Et_2O:pentane) gave the title compound as a clear oil (792 mg, 2.09 mmol, 95% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.58 – 7.37 (m, 2H), 7.37 – 7.22 (m, 3H), 5.70 (d, *J* = 5.4 Hz, 1H), 4.26 (q, *J* = 6.5 Hz, 1H), 3.83 (ddd, *J* = 12.6, 4.2, 2.5 Hz, 1H), 3.79 – 3.65 (m, 1H), 2.53 (td, *J* = 12.8, 5.6 Hz, 1H), 2.10 – 1.93 (m, 1H), 1.20 (dd, *J* = 6.6, 0.8 Hz, 3H), 1.11 – 0.96 (m, 9H), 0.85 – 0.59 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.2, 129.1, 127.2, 83.7, 70.9, 68.2, 58.6, 29.6, 17.4, 7.1, 5.3. HRMS: $[M + H]^+$ calculated for $C_{18}H_{30}N_3O_2Si$: 380.1828; found 380.1823.

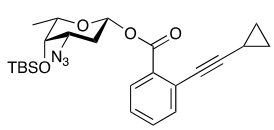
_o_-Cyclopropylethynylbenzoyl-3-azido-4-_O_-benzoyl-2,3-dideoxy-L-fucopyranoside (23)



To a solution of **17** (740 mg, 2 mmol) in MeCN:H_2O (18 mL, 10:1 v/v) was added *N*-iodosuccinimide (540 mg, 2.5 mmol, 1.25 eq) and the mixture was allowed to stir for 30 minutes. It was then diluted with EtOAc, washed with 10% aq. $Na_2S_2O_3$ and brine, and concentrated *in vacuo* to yield the lactol.

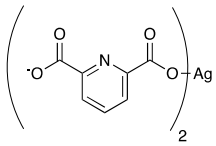
To a solution of the above crude lactol in DCM (5 mL) were added DIPEA (0.65 mL, 3.6 mmol, 1.8 eq), DMAP (244 mg, 2 mmol, 1 eq), EDCI·HCl (478 mg, 2.5 mmol, 1.25 eq) and freshly saponified *o*-cyclopropylethynylbenzoic acid **20** (478 mg, 2.5 mmol, 1.25 eq). After stirring overnight, the mixture was diluted with DCM and washed with sat. aq. $NaHCO_3$ and brine. Drying over $MgSO_4$, concentration *in vacuo* and column chromatography of the residue (5:95 – 15:85 EtOAc:pentane) gave the title compound as a thick clear oil (604 mg, 1.36 mmol, α:β 1:3.6, 68% over 2 steps). Spectral data for the α -anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.21 – 8.06 (m, 2H), 7.97 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.70 – 7.57 (m, 1H), 7.57 – 7.41 (m, 4H), 7.36 (td, *J* = 7.6, 1.5 Hz, 1H), 6.71 – 6.62 (m, 1H), 5.52 (d, *J* = 2.8 Hz, 1H), 4.45 (qd, *J* = 6.5, 1.3 Hz, 1H), 4.33 (ddd, *J* = 12.6, 4.8, 2.9 Hz, 1H), 2.41 (td, *J* = 13.1, 3.4 Hz, 1H), 2.23 (ddt, *J* = 13.4, 4.9, 1.5 Hz, 1H), 1.48 (tt, *J* = 8.2, 5.0 Hz, 1H), 1.23 (d, *J* = 6.5 Hz, 3H), 1.02 – 0.95 (m, 2H), 0.89 (ddt, *J* = 7.2, 5.0, 2.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 165.0, 135.0, 133.6, 132.2, 131.2, 131.1, 130.1, 129.4, 128.7, 127.5, 124.4, 99.0, 92.6, 75.3, 70.3, 68.5, 55.0, 29.0, 17.0, 9.1, 0.7. Spectral data for the β-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.27 – 8.11 (m, 2H), 8.02 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.64 – 7.56 (m, 1H), 7.56 – 7.41 (m, 4H), 7.33 (td, *J* = 7.6, 1.5 Hz, 1H), 6.13 – 6.04 (m, 1H), 5.42 (dd, *J* = 3.2, 1.2 Hz, 1H), 3.97 (qd, *J* = 6.4, 1.2 Hz, 1H), 3.82 (ddd, *J* = 12.0, 7.0, 3.2 Hz, 1H), 2.31 (td, *J* = 8.0, 7.4, 2.6 Hz, 2H), 1.59 – 1.47 (m, 1H), 1.29 (d, *J* = 6.4 Hz, 3H), 1.02 – 0.79 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 164.3, 134.4, 133.6, 132.3, 130.9, 130.5, 130.1, 129.3, 128.6, 127.1, 125.1, 99.9, 92.8, 74.5, 71.8, 69.3, 57.8, 30.4, 16.8, 8.9, 0.7. HRMS: $[M + Na]^+$ calculated for $C_{25}H_{23}N_3O_5Na$: 468.1535; found 468.1537.

o-Cyclopropylethynylbenzoyl-3-azido-2,3-dideoxy-4-tert-butyldimethylsilyl-L-fucopyranoside (24)



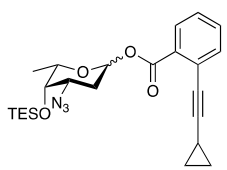
To a solution of **21** (483 mg, 1.27 mmol) in MeCN/H_2O (22 mL, 10:1 v/v) was added *N*-iodosuccinimide (357 mg, 1.59 mmol, 1.25 eq) and the mixture was allowed to stir for 30 minutes. It was then diluted with EtOAc, washed with 10% aq. $Na_2S_2O_3$ and brine, and concentrated in vacuo to yield the lactol. To a solution of this in DCM (6.4 mL) were added DIPEA (0.65 mL, 3.6 mmol, 1.8 eq), DMAP (153 mg, 1.27 mmol, 1 eq), EDCI·HCl (511 mg, 2.67 mmol, 3.2 eq) and freshly saponified o-cyclopropylethynylbenzoic acid **20** (763 mg, 3.81 mmol, 3 eq). After stirring overnight, the mixture was diluted with DCM and washed with sat. aq. $NaHCO_3$ and brine. Drying over $MgSO_4$, concentration in vacuo and column chromatography of the residue (2:98 – 10:90 EtOAc:pentane) gave the title compound as a thick clear oil (248 mg, 0.544 mmol, β only, 43% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.98 (dd, J = 7.9, 1.4 Hz, 1H), 7.48 (dd, J = 7.8, 1.4 Hz, 1H), 7.42 (td, J = 7.6, 1.4 Hz, 1H), 7.37 – 7.25 (m, 1H), 5.96 (dd, J = 9.7, 2.4 Hz, 1H), 3.65 (qd, J = 6.4, 1.1 Hz, 1H), 3.61 (dd, J = 2.6, 1.2 Hz, 1H), 3.56 (ddd, J = 12.5, 4.2, 2.6 Hz, 1H), 2.25 (td, J = 12.0, 9.8 Hz, 1H), 2.09 (dddd, J = 11.7, 4.3, 2.4, 0.9 Hz, 1H), 1.58 – 1.46 (m, 1H), 1.28 (d, J = 6.4 Hz, 3H), 0.97 (s, 10H), 0.90 – 0.87 (m, 4H), 0.20 (s, 3H), 0.11 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.5, 134.3, 132.1, 130.9, 130.8, 127.1, 125.1, 99.8, 93.2, 74.6, 73.3, 69.7, 60.0, 29.1, 26.2, 18.5, 17.8, 8.9, 0.7, -4.0, -4.4. HRMS: $[M + Na]^+$ calculated for $C_{24}H_{33}N_3O_4SiNa$; 478.21325; found 478.21286.

Silver(II) bis-(hydrogen dipicolinate) monohydrate [46]



To a suspension of $AgNO_3$ (10.1 g, 60.0 mmol) in H_2O (3 L) was added dipicolinic acid (20.0 g, 120 mmol, 2 eq). Potassium persulfate (81.0 g, 300 mmol, 5 eq) was added over the course of 2h and the reaction mixture was stirred for 2 days. The black precipitate was filtered off, washed with H_2O and dried high vacuum to afford the title compound as a black solid (25.8 g, 56.0 mmol, 94%).

***o*-Cyclopropylethynylbenzoyl-3-azido-2,3-dideoxy-4-triethylsilyl-L-fucopyranoside (25)**

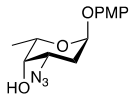


Method 1: To a solution of **22** (778 mg, 2.05 mmol) in MeCN/H_2O (35 mL, 10:1 v/v) was added *N*-iodosuccinimide (540 mg, 2.56 mmol, 1.25 eq) and the mixture was allowed to stir for 30 minutes. It was then diluted with EtOAc, washed with 10% aq. $Na_2S_2O_3$ and brine, and concentrated in vacuo to yield the lactol. To a solution of this in DCM (4.6 mL) were added DIPEA (1.3 mL, 7.2 mmol, 3.6 eq), DMAP (270 mg, 2.05 mmol, 1 eq), EDCI·HCl (845 mg, 4.42 mmol, 2.15 eq) and freshly saponified o-cyclopropylethynylbenzoic acid **20** (1.32 g, 6.6 mmol, 3.2 eq). After stirring overnight, the mixture was diluted with DCM and washed with sat. aq. $NaHCO_3$ and brine. Drying over $MgSO_4$, concentration in vacuo and column chromatography of the residue (1:99 - 2:98 EtOAc:pentane) gave the title compound as a white solid (191 mg, 0.42 mmol, β only, 20% over 2 steps).

Method 2: To a solution of **27** (583 mg, 1.48 mmol) in MeCN/H_2O (1:1 v/v, 80 mL) were added NaOAc (1.21 g, 14.8 mmol, 10 eq) and $Ag(DPAH)_2$ (2.71 g, 5.92 mmol, 4 eq) consecutively at 0°C. After stirring for 3 hours at that temperature, the reaction mixture was poured into sat. aq. $NaHCO_3$ and extracted with DCM twice. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give the crude hemiacetal as a yellow solid. (* Column chromatography of the intermediate hemiacetals resulting from silver(I)-mediated deprotection is advised, as residual silver salts effecting the cyclisation of alkynylbenzoic acids and esters was observed)

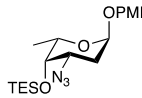
To a solution of the above hemiacetal in DCM (15 mL) were then added DMAP (183 mg, 1.48 mmol, 1 eq), DIPEA (1.16 mL, 6.67 mmol, 4.5 eq), EDCI·HCl (905 mg, 4.74 mmol, 3.2 eq) and freshly prepared *o*-cyclopropylethynylbenzoic acid **20** (827 mg, 4.44 mmol, 3 eq) and the mixture was stirred overnight. Thereafter, an equal portion of all reagents mentioned above was added again. After stirring another night, the reaction mixture was partitioned between sat. aq. $NaHCO_3$ and DCM, and the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (1.5:98.5) EtOAc:pentane and consecutive size-exclusion chromatography (Sephadex LH-20, eluent 1:1 DCM:MeOH) gave the title compound as a white solid (507 mg, 1.11 mmol, 75%, 1:5.5 α:β). Spectral data for the β-anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 7.1 Hz, 1H), 7.45 – 7.38 (m, 1H), 7.35 – 7.25 (m, 1H), 5.95 (dd, *J* = 9.7, 2.1 Hz, 1H), 3.70 – 3.52 (m, 3H), 2.25 (td, *J* = 12.0, 9.9 Hz, 1H), 2.08 (dt, *J* = 12.3, 3.5 Hz, 1H), 1.50 (h, *J* = 6.6 Hz, 1H), 1.28 (d, *J* = 6.4 Hz, 3H), 1.01 (t, *J* = 7.9 Hz, 9H), 0.94 – 0.83 (m, 4H), 0.71 (q, *J* = 7.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 148.4, 134.2, 132.0, 130.9, 130.7, 127.0, 125.0, 122.6, 99.8, 93.1, 73.1, 69.8, 60.0, 28.9, 17.4, 8.9, 7.1, 5.2, 0.7. Spectral data for the α-anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 7.6 Hz, 1H), 7.92 (d, *J* = 7.5 Hz, 1H), 7.55 (d, *J* = 7.4 Hz, 1H), 7.37 (s, 1H), 6.54 (d, *J* = 11.2 Hz, 1H), 4.17 – 4.01 (m, 1H), 3.76 (s, 1H), 2.36 (ddd, *J* = 12.9, 9.8, 3.4 Hz, 1H), 2.02 (dd, *J* = 12.6, 3.9 Hz, 1H), 1.46 – 1.40 (m, 1H), 1.37 (d, *J* = 6.9 Hz, 2H), 1.01 (t, *J* = 7.9 Hz, 9H), 0.94 – 0.83 (m, 4H), 0.71 (q, *J* = 7.6 Hz, 6H). HRMS: $[M + Na]^+$ calculated for $C_{24}H_{33}N_3O_4SiNa$ 478.21325; found 478.21286. IR (thin film, cm^{-1}): 2989, 2958, 2910, 2878, 2362, 2231, 2095 (N_3), 1724 (C=O), 1285, 1239.

***p*-Methoxyphenyl-4-O-acetyl-3-azido-2,3-dideoxy-α-L-fucopyranoside (26)**



15 (19.2 g, 59.8 mmol) was dissolved in MeOH (300 mL), to which NaOMe (650 mg, 12.0 mmol, 0.2 eq) was added. After stirring overnight, it was neutralized by addition of acetic acid and concentrated *in vacuo*. Column chromatography (15:85 - 30:70 EtOAc:pentane) gave the title compound as a light yellow solid (15.00 g, 53.7 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 – 6.92 (m, 2H), 6.92 – 6.79 (m, 2H), 5.55 (d, *J* = 3.0 Hz, 1H), 4.06 (q, *J* = 5.1 Hz, 1H), 4.01 (ddd, *J* = 12.3, 5.1, 2.8 Hz, 1H), 3.78 (s, 3H), 3.76 (d, *J* = 3.1 Hz, 1H), 2.21 (td, *J* = 12.7, 3.6 Hz, 1H), 2.11 (dd, *J* = 13.0, 5.1 Hz, 1H), 2.03 (d, *J* = 4.3 Hz, 1H), 1.24 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.9, 150.8, 117.6, 114.7, 96.2, 76.8, 69.8, 66.7, 57.1, 55.8, 29.0, 16.9. HRMS: $[M+Na]^+$ calculated for $C_{13}H_{17}N_3O_4Na$; 302.1111; found 302.1118.

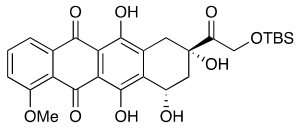
***p*-Methoxyphenyl-3-azido-2,3-dideoxy-4-triethylsilyl-α-L-fucopyranoside (27)**



To a solution of **26** (612 mg, 2.19 mmol) in DMF (3.7 mL) were added pyridine (0.53 mL, 6.6 mmol, 3 eq) and triethylsilyl triflate (0.89 mL, 3.9 mmol, 1.8 eq) at 0°C and the mixture was allowed to warm up to room temperature over 3 hours. It was then diluted with EtOAc and washed with H_2O thrice. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (pentane – 5:95 EtOAc:pentane) gave the title compound as a yellow oil (862 mg, 2.19 mmol, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, *J* = 8.0 Hz, 2H), 6.82 (d, *J* = 8.0 Hz, 2H), 5.56 (s, 1H), 4.04 (d, *J* =

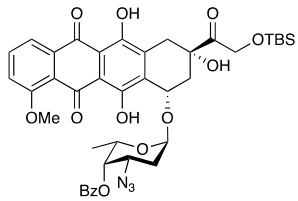
11.5 Hz, 1H), 3.94 (q, *J* = 6.3 Hz, 1H), 3.77 (s, 3H), 3.71 (s, 1H), 2.28 (t, *J* = 12.5 Hz, 1H), 2.01 (d, *J* = 10.9 Hz, 1H), 1.16 (d, *J* = 6.4 Hz, 3H), 1.07 – 0.91 (m, 9H), 0.80 – 0.62 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8, 151.0, 117.6, 114.7, 96.4, 76.9, 70.8, 67.9, 57.6, 55.8, 28.8, 17.6, 7.2, 5.4. HRMS: $[M + Na]^+$ calculated for $C_{19}H_{31}N_3O_4SiNa$ 416.19760; found 416.19727.

14-*O*-*tert*-butyldimethylsilyl-doxorubicinone (29)[40]



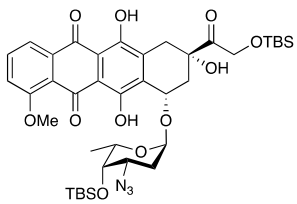
Commercially available doxorubicin hydrochloride (**1a**) (1.20 g, 2.07 mmol) was dissolved in 0.2M aq. HCl (120 mL) and heated to 90 °C. After stirring for 1.5 hours, the resulting solution was cooled to 0 °C, filtered and the filter was rinsed with MeOH, acetone and $CHCl_3$. This was combined with the filter residu and co-evaporated thrice with toluene to yield doxorubicinone **28**. This was then dissolved in DMF (10 mL), whereupon imidazole (366 mg, 5.38 mmol, 2.6 eq) and *tert*-butyldimethylsilyl chloride (315 mg, 2.09 mmol, 1.01 eq) were added consecutively. After stirring for 2.5 hours, additional imidazole (366 mg, 5.38 mmol, 2.6 eq) and *tert*-butyldimethylsilyl chloride (315 mg, 2.09 mmol, 1.01 eq) were added and stirring commenced for 30 minutes. The resulting solution was then diluted with DCM and the organic layer successively washed once with 1M aq. HCl and four times with H_2O, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (10:90 – 100:0 acetone:toluene) afforded the title compound as a dark red solid (1.06 g, 2.01 mmol, 97% over 2 steps). Spectral data was in accordance with that of literary precedence.[40]

7-[3-Azido-4-*O*-benzoyl-2,3-dideoxy-L-fucopyranoside]-14-O-tert-butyldimethylsilyl-doxorubicinone (30)



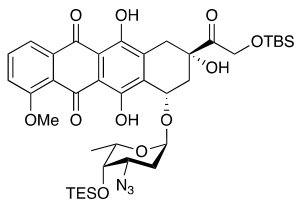
Prepared according to General Procedure A using donor **23** (α and/or β) and 14-*O*-TBS-doxorubicinone **29** (1-1.5 eq) at the desired temperature to give after column chromatography (10:90 EtOAc:pentane - 3:97 acetone:toluene) the title compound as a red solid. Spectral data for the α-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 14.05 (s, 1H), 13.29 (s, 1H), 8.06 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.87 – 7.75 (m, 1H), 7.41 (dd, *J* = 8.6, 1.1 Hz, 1H), 5.70 (d, *J* = 3.6 Hz, 1H), 5.44 (s, 1H), 5.36 – 5.30 (m, 1H), 4.89 (d, *J* = 1.6 Hz, 2H), 4.37 (s, 1H), 4.28 (q, *J* = 6.4 Hz, 1H), 4.10 (s, 3H), 3.83 (dt, *J* = 12.7, 4.2 Hz, 1H), 3.29 – 3.18 (m, 1H), 3.06 (d, *J* = 18.8 Hz, 1H), 2.39 – 2.29 (m, 1H), 2.29 – 2.16 (m, 2H), 2.04 (dd, *J* = 13.2, 5.1 Hz, 1H), 1.31 – 1.20 (m, 3H), 0.96 (s, 9H), 0.15 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.0, 187.4, 186.9, 161.2, 156.4, 155.9, 136.0, 135.7, 134.1, 133.6, 129.5, 129.4, 129.3, 120.0, 118.6, 111.8, 111.6, 100.8, 70.4, 70.2, 66.8, 66.7, 56.9, 54.9, 35.8, 34.1, 29.8, 26.0, 17.0. HRMS: $[M + Na]^+$ calculated for $C_{40}H_{45}N_3O_{12}SiNa$ 810.26702; found 810.2675.

7-[3-Azido-4-*O*-*tert*-butyldimethylsilyl-2,3-dideoxy-L-fucopyranoside]-14-O-tert-butyldimethylsilyl-doxorubicinone (31)



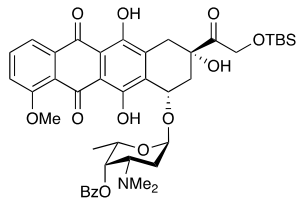
Prepared according to General Procedure A using donor **24** (90 mg, 0.198 mmol) and 14-*O*-TBS-doxorubicinone **29** (158 mg, 0.299 mmol, 1.5 eq) at RT to give after column chromatography (5:95 EtOAc:pentane – 2:98 - 20:80 acetone:toluene) the title compound as a red solid (125 mg, 0.157 mmol, 78%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.90 (s, 1H), 13.15 (s, 1H), 7.98 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.76 (t, *J* = 8.1 Hz, 1H), 7.39 (dd, *J* = 8.6, 1.1 Hz, 1H), 5.54 (d, *J* = 3.7 Hz, 1H), 5.22 (dd, *J* = 4.3, 2.1 Hz, 1H), 4.87 (d, *J* = 1.5 Hz, 2H), 4.48 (s, 1H), 4.08 (s, 3H), 3.96 (q, *J* = 6.5 Hz, 1H), 3.68 (d, *J* = 2.4 Hz, 1H), 3.60 (ddd, *J* = 12.8, 4.4, 2.4 Hz, 1H), 3.15 (dd, *J* = 18.9, 2.0 Hz, 1H), 2.88 (d, *J* = 18.8 Hz, 1H), 2.32 (dt, *J* = 14.8, 2.1 Hz, 1H), 2.25 – 2.08 (m, 2H), 1.83 (dd, *J* = 12.7, 4.3 Hz, 1H), 1.24 (d, *J* = 6.5 Hz, 3H), 0.96 (s, 18H), 0.19 – 0.11 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.2, 187.0, 186.7, 161.1, 156.4, 155.7, 135.8, 135.5, 134.0, 133.8, 120.8, 119.9, 118.6, 111.5, 111.4, 101.0, 70.4, 70.1, 68.4, 66.7, 57.3, 56.8, 35.6, 33.9, 28.4, 26.1, 26.0, 18.7, 18.5, 17.9, -4.1, -4.3, -5.3. HRMS: $[M + Na]^+$ calculated for $C_{39}H_{55}N_3O_{11}Si_2Na$ 820.32673; found 820.32770.

7-[3-Azido-2,3-dideoxy-4-triethylsilyl-L-fucopyranoside]-14-O-tert-butyldimethylsilyl-doxorubicinone (32)



Prepared according to General Procedure A using donor **25** (191 mg, 0.419 mmol) and 14-O-TBS-doxorubicinone **29** (369 mg, 0.698 mmol, 1.67 eq) at RT to give after column chromatography (10:90 EtOAc:pentane and then 3:97 acetone:toluene) the title compound as a red solid (246 mg, 0.308 mmol, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.95 (s, 1H), 13.25 (s, 1H), 8.11 – 7.95 (m, 1H), 7.78 (t, *J* = 8.1 Hz, 1H), 7.40 (d, *J* = 8.1 Hz, 1H), 5.56 (d, *J* = 3.3 Hz, 1H), 5.33 – 5.22 (m, 1H), 4.88 (d, *J* = 1.9 Hz, 2H), 4.50 (s, 1H), 4.09 (s, 3H), 3.95 (q, *J* = 6.4 Hz, 1H), 3.69 (s, 1H), 3.62 (ddd, *J* = 12.7, 4.2, 2.4 Hz, 1H), 3.22 (dd, *J* = 18.9, 1.5 Hz, 1H), 2.98 (d, *J* = 18.8 Hz, 1H), 2.32 (d, *J* = 14.8 Hz, 1H), 2.22 – 2.12 (m, 2H), 1.82 (dd, *J* = 12.7, 4.3 Hz, 1H), 1.24 (d, *J* = 6.5 Hz, 3H), 1.05 – 0.91 (m, 18H), 0.77 – 0.66 (m, 6H), 0.14 (d, *J* = 1.5 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.2, 187.2, 161.2, 156.4, 155.9, 135.9, 135.6, 133.9, 121.0, 111.5, 101.0, 70.6, 70.0, 68.3, 66.8, 57.3, 56.8, 35.7, 34.0, 28.4, 26.0, 17.6, 7.1, 5.4. HRMS: $[M + Na]^+$ calculated for $C_{39}H_{55}N_3O_{11}Si_2Na$ 820.32673; found 820.32770.

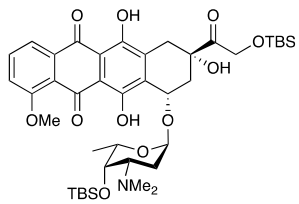
7-[3-Dimethylamino-4-*O*-benzoyl-2,3-dideoxy-L-fucopyranoside]-14-O-tert-butyldimethylsilyl-doxorubicinone (33)



To a solution of **30** (20.4 mg, 25.9 µmol) in THF/H_2O (1.8 mL, 10:1 v/v) was added polymer-supported triphenylphosphine (3 mmol/g loading, 26 mg, 52 µmol, 2 eq) and the mixture was stirred overnight. Then, additional polymer-supported triphenylphosphine (26 mg, 52 µmol, 2 eq) was added and the mixture was allowed to stir another night. It was then filtered off and concentrated *in vacuo*. Column chromatography (20:80 acetone:toluene) gave the amine as a red solid (9.5 mg, 0.013 mmol, 48%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 14.00 (s, 1H), 13.28 (s, 1H), 8.15 – 8.10 (m, 2H), 8.06 – 8.02 (m, 1H), 7.79 (t, *J* = 8.1 Hz, 1H), 7.64 – 7.57 (m, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.40 (d, *J* = 8.3 Hz, 1H), 5.64 (s, 1H), 5.34 (d, *J* = 3.3 Hz, 1H), 5.28 (d, *J* = 2.7 Hz, 1H), 5.00 – 4.83 (m, 2H), 4.26 (q, *J* = 6.4 Hz, 1H), 4.19 – 3.99 (m, 4H), 3.25 (dd, *J* = 18.8, 1.9 Hz, 2H), 3.04 (d, *J* = 18.9 Hz, 1H), 2.39 – 2.13 (m, 4H), 1.30 – 1.19 (m, 3H), 0.96 (s, 9H), 0.15 (s, 6H). HRMS: $[M + Na]^+$ calculated for $C_{40}H_{47}NO_{12}SiNa$ 762.2946; found 762.2946.

The above amine (9.5 mg, 12.5 µmol) was dissolved in EtOH (3.0 mL) and 37% aq. CH_2O (28 µL, 344 µmol, 27.5 eq) by sonication for 30 minutes. To this solution was then added $NaBH(OAc)_3$ (8.74 mg, 41.3 µmol, 1.95 eq) and it was stirred for 3 hours. The mixture was then poured into sat. aq. $NaHCO_3$, extracted twice with DCM and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography (5:95 – 30:70 acetone:toluene) gave the title compound as a red solid (5.2 mg, 6.58 µmol, 53%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 14.01 (s, 1H), 13.29 (s, 1H), 8.13 – 8.09 (m, 2H), 8.05 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.83 – 7.77 (m, 1H), 7.62 – 7.56 (m, 1H), 7.47 (dd, *J* = 8.4, 7.1 Hz, 2H), 7.41 (dd, *J* = 8.6, 1.1 Hz, 1H), 5.69 (d, *J* = 3.7 Hz, 1H), 5.53 (s, 1H), 5.33 (dd, *J* = 4.1, 2.1 Hz, 1H), 4.93 (d, *J* = 3.5 Hz, 2H), 4.68 (s, 1H), 4.20 (q, *J* = 6.5 Hz, 1H), 4.10 (s, 3H), 3.25 (dd, *J* = 19.0, 1.9 Hz, 1H), 3.05 (d, *J* = 18.9 Hz, 1H), 2.50 (d, *J* = 12.4 Hz, 1H), 2.37 (dd, *J* = 14.9, 2.3 Hz, 1H), 2.27 – 2.17 (m, 7H), 2.11 (td, *J* = 13.0, 4.1 Hz, 1H), 1.96 (dd, *J* = 13.1, 4.2 Hz, 1H), 1.20 (d, *J* = 6.5 Hz, 3H), 0.97 (s, 9H), 0.15 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.3, 187.3, 186.9, 166.4, 161.2, 156.6, 156.0, 135.9, 135.7, 134.2, 134.1, 133.3, 130.1, 128.6, 121.1, 120.0, 118.5, 111.6, 111.5, 101.7, 70.2, 69.3, 67.5, 66.8, 59.4, 56.9, 42.7, 35.8, 34.1, 29.6, 26.0, 17.3. HRMS: $[M + Na]^+$ calculated for $C_{42}H_{51}NO_{12}SiNa$ 790.3259; found 790.3256.

7-[3-Dimethylamino-4-*O*-*tert*-butyldimethylsilyl-2,3-dideoxy-L-fucopyranoside]-14-O-tert-butyldimethylsilyl-doxorubicinone (34)

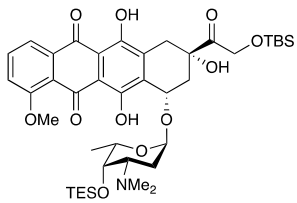


To a solution of **31** (115 mg, 0.144 mmol) in THF/H_2O (11 mL, 10:1 v/v) was added polymer-supported triphenylphosphine (3 mmol/g loading, 480 mg, 1.44 mmol, 10 eq) and the mixture was stirred overnight at 50°C. It was then filtered off and concentrated *in vacuo*. Column chromatography (2:98 – 100:0 acetone:toluene) gave the amine as a red solid (82.8 mg, 0.107 mmol, 75%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.90 (s, 1H), 8.00 (d, *J* = 7.6 Hz, 1H), 7.77 (t, *J* = 8.1 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 5.47 (d, *J* = 3.8 Hz, 1H), 5.32 – 5.19 (m, 1H), 4.89 (d, *J* = 2.0 Hz, 2H), 4.78 (s, 1H), 4.09 (s, 3H), 3.97 (q,

J = 6.5 Hz, 1H), 3.60 (d, *J* = 2.3 Hz, 1H), 3.18 (dd, *J* = 18.9, 2.0 Hz, 1H), 2.96 (d, *J* = 18.9 Hz, 1H), 2.90 (dt, *J* = 12.0, 3.4 Hz, 1H), 2.33 (dt, *J* = 14.8, 2.2 Hz, 1H), 2.13 (dd, *J* = 14.7, 4.0 Hz, 1H), 1.83 (td, *J* = 12.8, 4.0 Hz, 1H), 1.60 (dd, *J* = 13.0, 4.3 Hz, 2H), 1.23 (d, *J* = 6.5 Hz, 3H), 0.97 (d, *J* = 3.0 Hz, 18H), 0.14 (dd, *J* = 5.4, 1.5 Hz, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.5, 187.1, 186.7, 161.1, 156.5, 155.9, 135.8, 135.6, 134.3, 134.1, 121.0, 119.9, 118.5, 111.5, 111.3, 101.6, 73.4, 69.6, 68.8, 66.7, 56.8, 47.7, 35.6, 34.1, 34.0, 26.3, 26.0, 18.7, 18.6, 18.2, -3.4, -3.6, -5.2, -5.3.

The above amine (32.9 mg, 42.6 µmol) was dissolved in a stock solution of ethanolic formaldehyde (2.1 mL, prepared by dissolving 31.7 µL of 37% aqueous formaldehyde in 21 mL EtOH). To this solution was then added $NaBH(OAc)_3$ (15.4 mg, 41.3 µmol, 1.7 eq) and it was then stirred for 3 hours. The mixture was then poured into sat. aq. $NaHCO_3$, extracted twice with DCM and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography (4:96 acetone:toluene) gave the title compound as a red solid (15.3 mg, 19.1 µmol, 45%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.93 (s, 1H), 13.29 (s, 1H), 8.03 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.78 (t, *J* = 8.1 Hz, 1H), 7.39 (dd, *J* = 8.5, 1.1 Hz, 1H), 5.51 (d, *J* = 3.5 Hz, 1H), 5.26 (dd, *J* = 4.0, 2.1 Hz, 1H), 4.91 (d, *J* = 1.6 Hz, 2H), 4.86 (s, 1H), 4.09 (s, 3H), 3.90 (q, *J* = 6.4 Hz, 1H), 3.73 (s, 1H), 3.21 (dd, *J* = 18.9, 1.9 Hz, 1H), 3.03 (d, *J* = 18.9 Hz, 1H), 2.45 – 2.25 (m, 2H), 2.13 (d, *J* = 6.5 Hz, 7H), 1.98 (d, *J* = 15.4 Hz, 2H), 1.74 – 1.54 (m, 3H), 1.25 – 1.23 (m, 3H), 0.95 (d, *J* = 10.0 Hz, 18H), 0.18 – 0.04 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.6, 187.3, 186.8, 161.2, 156.7, 156.1, 135.8, 135.7, 134.2, 119.9, 118.5, 111.5, 111.4, 101.9, 69.8, 69.6, 69.2, 66.8, 56.8, 42.9, 35.7, 34.0, 29.8, 26.3, 26.0, 18.9, 18.7, 18.3, -5.1, -5.2. HRMS: $[M + H]^+$ calculated for $C_{41}H_{62}NO_{11}Si_2$ 800.38559; found 800.38605.

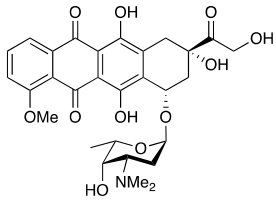
7-[3-Dimethylamino-2,3-dideoxy-4-triethylsilyl-L-fucopyranoside]-14-O-tert-butyldimethylsilyl-doxorubicinone (35)



To a solution of **32** (620 mg, 0.777 mmol) in THF/H_2O (10:1 v/v, 56 mL) was added polymer-supported triphenylphosphine (2.59 g, 7.8 mmol, 10 eq) and the resulting mixture was stirred at 50 °C for 3 days. It was then filtered, concentrated *in vacuo* and coevaporated with toluene thrice. Column chromatography (6:94 acetone:toluene) gave the free amine as a red solid (451 mg, 0.584 mmol, 75%) which was used immediately in the next step.

The above free amine (51 mg, 66 µmol) was then dissolved in EtOH (4.2 mL) and 37% aq. CH_2O (147 µL, 1.82 mmol, 27.5 eq) by sonication for 30 minutes. To this solution was then added $NaBH(OAc)_3$ (27.3 mg, 0.129 mmol, 1.95 eq) and it was then stirred for 1.5 hours. The mixture was then poured into sat. aq. $NaHCO_3$, extracted twice with DCM and the combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography (5:95 – 20:80 acetone:toluene) gave the title compound as a red solid (44 mg, 55 µmol, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.92 (s, 1H), 13.27 (s, 1H), 8.02 (d, *J* = 7.5 Hz, 1H), 7.77 (t, *J* = 8.1 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 5.51 (d, *J* = 3.4 Hz, 1H), 5.25 (s, 1H), 4.91 (d, *J* = 3.0 Hz, 2H), 4.86 (s, 2H), 4.09 (s, 3H), 3.88 (q, *J* = 6.5 Hz, 1H), 3.73 (s, 1H), 3.20 (d, *J* = 18.9 Hz, 1H), 3.01 (d, *J* = 18.9 Hz, 1H), 2.36 (d, *J* = 14.6 Hz, 1H), 2.14 (s, 6H), 2.11 – 2.07 (m, 1H), 1.97 (td, *J* = 12.9, 4.0 Hz, 1H), 1.67 (d, *J* = 9.6 Hz, 1H), 1.24 (d, *J* = 6.9 Hz, 3H), 1.07 – 0.77 (m, 18H), 0.77 – 0.52 (m, 6H), 0.14 (d, *J* = 1.9 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.6, 187.2, 186.8, 161.1, 156.6, 156.0, 135.8, 135.7, 134.5, 134.2, 121.1, 119.9, 118.5, 111.5, 111.4, 101.8, 69.7, 69.6, 69.1, 66.8, 61.4, 42.9, 35.7, 34.0, 28.0, 26.0, 18.7, 18.0, 7.3, 5.6. HRMS: $[M + H]^+$ calculated for $C_{41}H_{62}NO_{11}Si_2$ 800.38559; found 800.38605.

***N,N*-dimethyldoxorubicin (3a)**



To a solution of **35** (81 mg, 0.10 mmol) in THF (7 mL) and pyridine (3.5 mL) at 0 °C was added HF·pyr complex (70 wt% HF, 420 µL). The mixture was stirred for 30 minutes at that temperature, after which it was allowed to stir for 3 hours at room temperature. Solid $NaHCO_3$ was added to quench and the mixture was stirred until cessation of effervescence. It was then filtered off, and THF was removed from the filtrate *in vacuo*. The crude product, still dissolved in pyridine, was subjected to column chromatography on neutral silica (DCM – 80:20 MeOH:DCM) to yield *N,N*-dimethyldoxorubicin (**2**) as a red solid (38 mg, 67 µmol, 66%). ^{1}H NMR (500 MHz, MeOD) δ 7.66 (t, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 5.42 (d, *J* = 3.4 Hz, 1H), 4.95 (s, 1H), 4.80 – 4.65 (m, 1H), 4.14 (q, *J* = 6.5 Hz, 1H), 3.92 (s, 2H), 3.83 (d, *J* = 6.0 Hz, 1H), 2.94 (d, *J* = 18.1 Hz, 1H), 2.68 (d, *J* = 18.3 Hz, 1H), 2.62 (d, *J* = 11.9 Hz, 1H), 2.42 (s, 3H), 2.29 (t, *J* = 13.1 Hz, 1H), 2.10

– 2.02 (m, 2H), 1.94 (td, *J* = 13.1, 4.1 Hz, 1H), 1.30 (d, *J* = 6.5 Hz, 2H). ^{13}C NMR (126 MHz, MeOD) δ 214.43, 187.37, 162.20, 157.08, 155.85, 137.03, 135.86, 135.40, 134.85, 121.03, 120.34, 112.11, 111.87, 102.06, 77.41, 70.94, 68.89, 67.80, 65.71, 62.28, 57.00, 49.51, 49.34, 49.17, 49.00, 48.83, 48.66, 48.49, 42.40, 36.86, 33.88, 28.63, 17.29. HRMS: $[M + H]^+$ calculated for $C_{29}H_{34}NO_{11}$ 572.21249; found 572.21246.

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Chapter 3

Design and synthesis of doxorubicin/aclarubicin hybrids

Introduction

Anthracyclines comprise one of the most successful classes of natural products in history from which chemotherapeutic agents have been derived.[1] Two archetypal anthracyclines are doxorubicin (**1**, Figure 1) and aclarubicin, also known as aclacinomycin A[2] (**12**), both effective anti-cancer agents that have been used for several decades in the clinic.[3] Today doxorubicin is prescribed in the Western world for the treatment of a variety of cancers. Aclarubicin finds widespread use in Asia, also for combating various cancers.[4] Although structurally closely related, doxorubicin and aclarubicin feature a few notable differences in both their glycan and aglycon moieties. These structural differences that cause anthracyclines to display distinct biological activities are at the basis of the remarkable (though as of yet poorly understood) differences in their clinical manifestation. Doxorubicin induces severe cumulative cardiotoxicity, and clinical treatment with doxorubicin is therefore limited to six to eight doses.[5–7] In contrast, aclarubicin is more than a tenfold less cardiotoxic[8] and recent research by the group of Neefjes has provided evidence that this difference in toxicity may be related to the differences in the modes of action of the two compounds.[9] Doxorubicin causes disruption of chromatin structure by inducing histone eviction, and causes DNA double strand cleavages. Aclarubicin is capable of evicting histones as well, but DNA strands remain unaffected in cells treated with this agent. Furthermore, the non-cardiotoxic chemotherapeutic agent etoposide is able to induce DNA breaks but not histone eviction. This has led to the hypothesis that anthracyclines that effect both DNA double strand cleavage and histone eviction are cardiotoxic, whereas histone eviction alone suffices for anticancer activity.

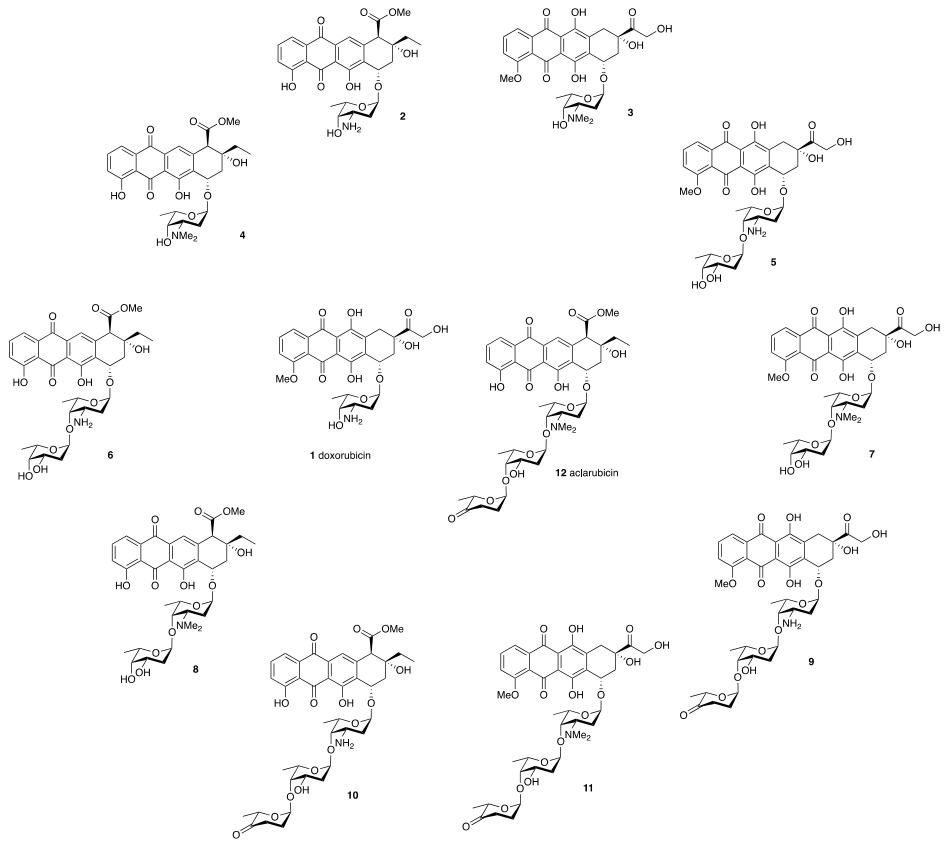
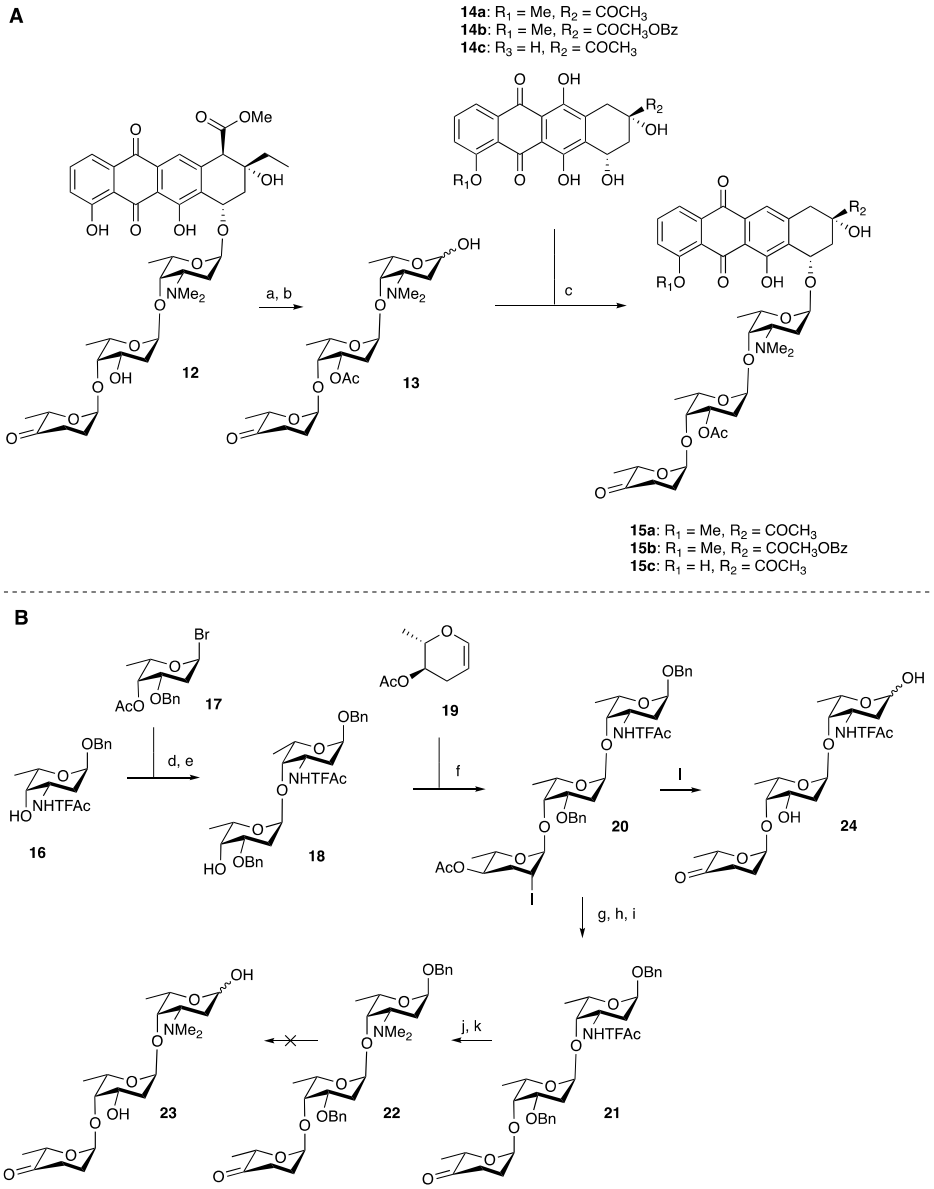


Figure 1. Chemical structures of doxorubicin (**1**), aclarubicin (**12**) and hybrid structures **2** – **11** subject of this Chapter.

Structural differences between doxorubicin and aclarubicin that may cause the diverging biological activities, can be divided into three categories: variation in the anthraquinone aglycon, in the (length of the) carbohydrate fragment and in the substitution pattern of the sole amine in both compounds. The anthraquinone portions have the same general architecture but vary at places in substitution/oxidation pattern. Doxorubicin features an α-L-daunosamine as the single, monosaccharidic carbohydrate fragment. Aclarubicin features an α-L-rhodosamine (*N*,*N*-dimethyldaunosamine), that is further glycosylated on its 4-hydroxyl function with an α-(1→4) disaccharide composed of L-oliose and L-cinerulose A. The differences in activity of doxorubicin and aclarubicin may be due to the difference in the overall architecture, or to one of the three distinguishing features as outlined above: the variant aglycon, the lack of *N*-methylation or the lack of additional deoxyfucose sugars. In order to assess whether distinct structural differences are at the basis of the divergent activity, a set of doxorubicin/aclarubicin hybrids (**2** – **11**, Figure 1) was designed, which comprises

anthracyclines composed of either of the two aglycons featuring a monosaccharide, a disaccharide or a trisaccharide glycan composed of the sugar configurations found in the parent structures, and with the amines bearing no or two methyl substituents.



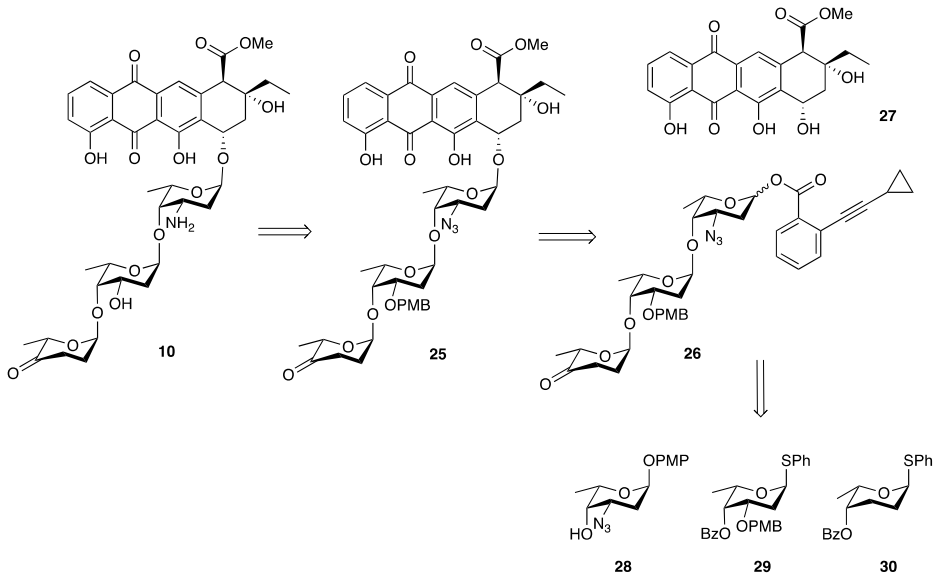
Scheme 1. Reported syntheses of the trisaccharide moiety found in aclarubicin (**12**). *Reagents and conditions:* (a) Ac_2O, pyr., 96%; (b) Pd/$BaSO_4$, MeOH, 98%; (c) Tf_2O, TBABr, *sym*-collidine, -70 °C, 33% for **15a**, 32% for **15b**, 20% for **15c**; (d) Ag_2O, $HgBr_2$, DCM, 0 °C to RT, 40%; (e) NaOMe, MeOH, 97%; (f) NIS, MeCN, 0 °C, 68%; (g) Pd/C, Et_3N, EtOH, 87%; (h) NaOMe, MeOH, 95%; (i) pyridinium dichromate, DCM, 91%; (j) K_2CO_3, MeOH, H_2O, 68%; (k) aq. CH_2O, $NaBH_3CN$, MeCN, 90%; (l) Pd/C, EtOAc, 85%.

Although the synthesis of anthraquinone monosaccharides has gathered considerable attention[10], only few studies on the synthesis of the di- and trisaccharide motifs discussed in this Chapter have been reported. Tanaka and co-workers, who reported the isolation and structure of aclarubicin (**12**), described the cleavage of the trisaccharide moiety from the parent drug for use in glycosylation to different aglycons.[11] They accomplished this feat by acetylation and hydrogenation ($Pd/BaSO_4$) of aclarubicin (**12**) to yield the (3'-) protected trisaccharide hemi-acetal **13**. Anomeric triflation in the presence of tetra-*n*-butylammonium bromide (TBABr) and *sym*-collidine was followed by addition of aglycones **14a**-**14c** to yield the corresponding anthraquinone trisaccharides **15a**-**15c**. Although this gave quick access to the desired compounds, the yields of these glycosylations were modest (20-33%) and did not allow for variations on the trisaccharide (i.e. free amine or shorter saccharide chain) nor did it result in any methodology on assembling the trisaccharide itself. Monneret *et al*. synthesized the protected trisaccharide found in aclarubicin in 1988.[12] Glycosylation of L-oliosyl bromide **17** under Koenigs-Knorr conditions to L-daunosaminyl acceptor **16** yielded the desired orthogonally protected disaccharide α-selectively in 40% yield. Deacetylation yielded **18** and was followed by addition of L-amicetosyl glycal **19** in the presence of *N*-iodosuccinimide to yield **20**. Removal of the 2"-iodide through hydrogenolysis was followed by Zemplén conditions (NaOMe, MeOH) to remove the 4"-acetyl, followed by pyridinium dichromate oxidation of the resultant alcohol to yield orthogonally protected cineruloside **21**. Removal of the trifluoroacetyl (K_2CO_3, MeOH) followed by reductive alkylation yielded protected aclarubicin trisaccharide **22**. Removal of the remaining benzyl groups to give **23** was unsuccessful and instead hydrogenolysis before installation of the dimethylamino motif was suggested, to yield *N*-trifluoroacetylated **24**, which is to be dimethylated post-glycosylation. Overall, the authors were able to prepare the trisaccharide motif but did not report on glycosylation studies with donor glycosides derived from the trisaccharide.

This Chapter describes the design and synthesis of a focused library of mono-, di- and trisaccharides filling the chemical space between doxorubicin (**1**) and aclarubicin (**12**). The synthesis strategy relies on α-selective iterative IDCP-mediated thioglycosylations to assemble the trisaccharide motif. Glycosylation to the anthraquinone moiety was accomplished by a method developed in the group of Yu (see also Chapter 2), wherein anomeric *ortho*-alkynylbenzoates are used as glycosylating agents in the presence of catalytic amounts of gold(I) species.

Results and discussion

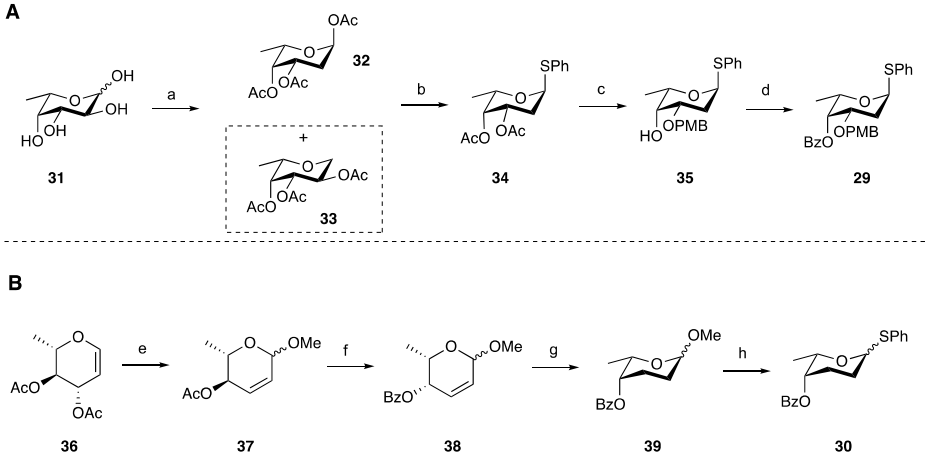
The retrosynthetic analysis for **10**, representative for the compounds prepared in this Chapter, is outlined in Scheme 2.



Scheme 2. Retrosynthesis of trisaccharide **10**, representative for the compounds prepared in this Chapter.

Orthogonally protected trisaccharide **25** contains a *p*-methoxybenzyl group on the 3''-hydroxyl function with the 3'-amine masked as an azide. Disconnection of the trisaccharide and the aglycon shows that *ortho*-alkynylbenzoate donor **26** can be attached to aklavinone (**27**, the aglycone found in aclarubicin) by means of the gold catalysis chemistry described in Chapter 2. The assembly of the trisaccharide motif may be effected by iterative IDCP-mediated thioglycosylations of L-daunosaminyl acceptor **28** (described in Chapter 2), L-oliosyl donor **29** and L-rhodinosyl donor **30**. The latter building blocks **29** and **30** are equipped with a C4-benzoate, allowing for long-range participation during the glycosylation reactions. Rhodinoside **30** serves as a precursor for the desired cinerulose moiety at the non-reducing end of the trisaccharide in **10**. The anomeric *p*-methoxyphenolate (OPMP) can be removed under mild oxidative conditions, thereby enabling introduction of the anomeric *ortho*-alkynylbenzoates required for the glycosylation reactions.

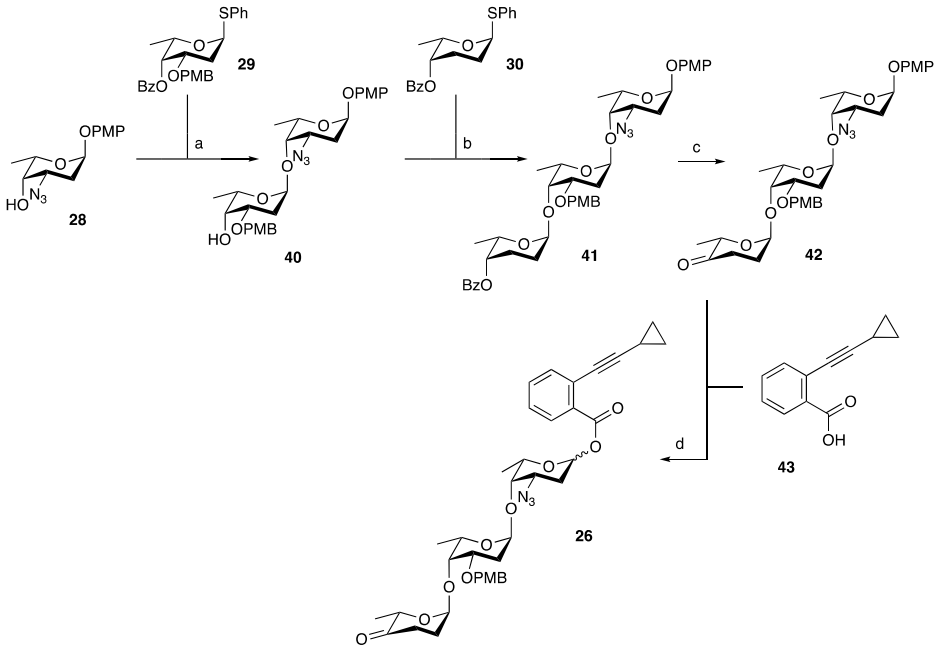
The synthesis of L-oliosyl donor **29** is depicted in Scheme 3A. According to the procedure reported by Gildersleeve *et al.*[13], L-fucose was transformed by sequential peracetylation, anomeric bromination (HBr) and radical-induced 1,2-*cis* migration



Scheme 3. Preparation of L-olioside and L-rhodinoside donors **29** and **30**. *Reagents and conditions:* (a) *i.* Ac_2O, pyr.; *ii.* HBr/AcOH, DCM; *iii.* Bu_3SnH, AIBN, toluene, 80 °C, 48% over 3 steps; (b) PhSH, $BF_3{\cdot}OEt_2$, DCM, -78 °C to 0 °C, 94% (10:1 α:β); (c) *i.* NaOMe, MeOH; *ii.* Bu_2SnO, toluene, 140 °C, then PMB-Cl, TBABr, toluene, 100 °C, o.n., 96% over 2 steps; (d) BzCl, pyr., DCM, 82%; (e) MeOH, $SnCl_4$, DCM, 80% (6:1 α:β); (f) *i.* NaOMe, MeOH; *ii.* benzoic acid, DEAD, PPh_3, THF, 0 °C, 70% over 2 steps (6:1 α:β); (g) Pd black, H_2, MeOH, 91%; (h) PhSH, $BF_3{\cdot}OEt_2$, DCM, -78 °C to -15 °C, 80% (α:β 1.2:1).

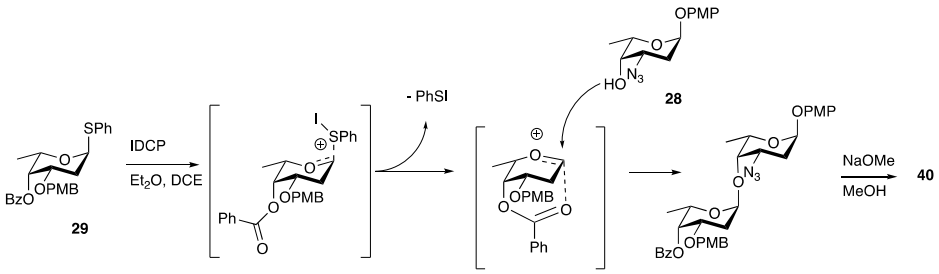
(Bu_3SnH, AIBN) of the 2-*O*-acetyl group to 2-deoxyfucoside **32**. In the latter step, the desired product was obtained together with tetrahydropyran **33** as a 3:1 mixture, as a result of quenching of the intermediate anomeric radical by tributyltin hydride *before* the 1,2-*cis*-migration - a phenomenon that was not observed by Gildersleeve and co-workers.[13] Regio-isomer **33** could be removed by crystallisation from ethanol. Next, installment of an anomeric thiophenyl group (PhSH, $BF_3{\cdot}OEt_2$) gave **34** as a 10:1 α:β mixture. Removal of the acetyl groups in **34** under Zemplén conditions was followed by installation of the 3-*O*-*p*-methoxybenzyl group using stannylene-acetal chemistry to yield **35** near quantitatively. A final benzoylation of the remaining 4-hydroxyl function yielded L-oliosyl donor **29**.

The synthesis of L-rhodinosyl donor **30** (Scheme 3B) commenced with L-rhamnal **36** (prepared in Chapter 2), using a method developed by Bhaté *et al*.[14] In this step, the C-3-acetate is eliminated in a Lewis acid mediated Ferrier rearrangement[15], after which methanol can attack the anomeric centre yielding methyl-*eno*-pyranoside **37**. This synthon was then deacetylated, after which the resulting allylic alcohol was subjected to a Mitsunobu-inversion with benzoic acid to give **38**.[16] Palladium-catalyzed hydrogenation of the double bond yielded the rhodinose-motif, after which installation of an anomeric thiophenyl moiety (PhSH, $BF_3{\cdot}OEt_2$, -78 °C to 0 °C) delivered donor **30** as a separable 1.2:1 α:β mixture.



Scheme 4. Preparation of trisaccharide *ortho*-alkynylbenzoate donor **26**. *Reagents and conditions:* (a) *i.* IDCP, Et_2O, DCE (4:1 v/v); *ii.* NaOMe, MeOH, 85% over 2 steps (α-only); (b) IDCP, Et_2O, DCE (4:1 v/v), 92% (α-only); (c) *i.* NaOMe, MeOH; *ii.* Dess-Martin periodinane, $NaHCO_3$, DCM, 98% over 2 steps; (d) *i.* Ag(II)(hydrogen dipicolinate)$_2$, NaOAc, MeCN, H_2O, 0 °C; *ii.* EDCI·HCl, DIPEA, DMAP, DCM, 75% over 2 steps (2:3 α:β).

With the three building blocks **28**, **29** and **30** in hand, the synthesis of trisaccharide alkynylbenzoate donor **26** was undertaken as shown in Scheme 4. For the construction of the glycosidic linkages of the reactive and relatively acid labile 2,6-dideoxy and 2,3,6-trideoxyglycosides, iodonium di-collidinium perchlorate (IDCP) was explored as this reagent has previously been used for the synthesis of anthraquinone 2-deoxy saccharides[17] and for the activation of other reactive glycosyl donors.[18] Advantageous to this activation system is that it does not require addition of a strong (Lewis-) acid which can be detrimental to the 2-deoxy glycosidic bonds. Additionally, the reaction is buffered by the release of two equivalents of *sym*-collidine per donor activation event. Activation of thioglycoside **29** in the presence of acceptor **28** and IDCP in Et_2O/DCE stereoselectively yielded α-(1→4) linked disaccharide **40** after debenzoylation under Zemplén conditions. A stereochemical rationale for this selectivity is outlined in Scheme 5.

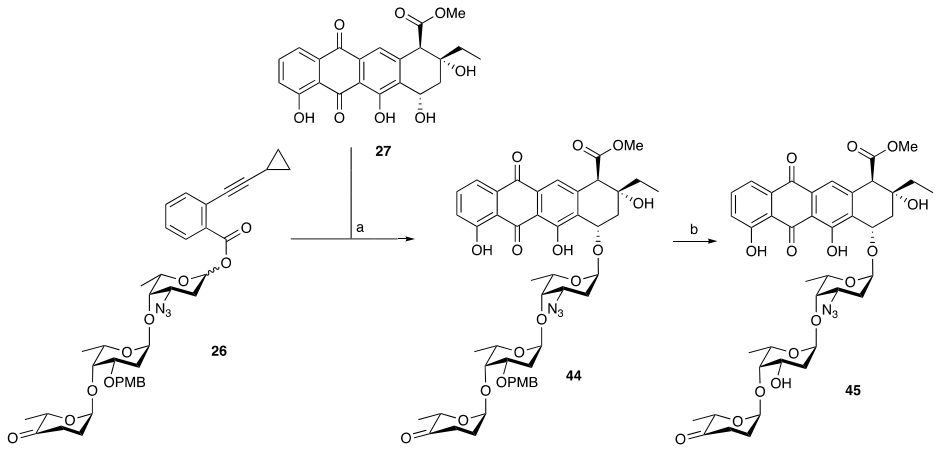


Scheme 5. Stereochemical rationale for α-glycosidic bond formation in **40**.

Upon treatment of donor **29** with IDCP, the formed oxocarbenium ion may be stabilized by electron density donation of the carbonyl of the 4-benzoate group as depicted in Scheme 5. The bottom face of the so-formed dioxolenium ion-like species is blocked, forcing acceptor **28** to attack the top face. The acceptor features a relatively poorly nucleophilic axial alcohol, with its reactivity further lowered by the neighboring 3-azide. In general, the decrease of acceptor nucleophilicity has been shown to promote α-selective glycosylations, possibly also taking place here.[19]

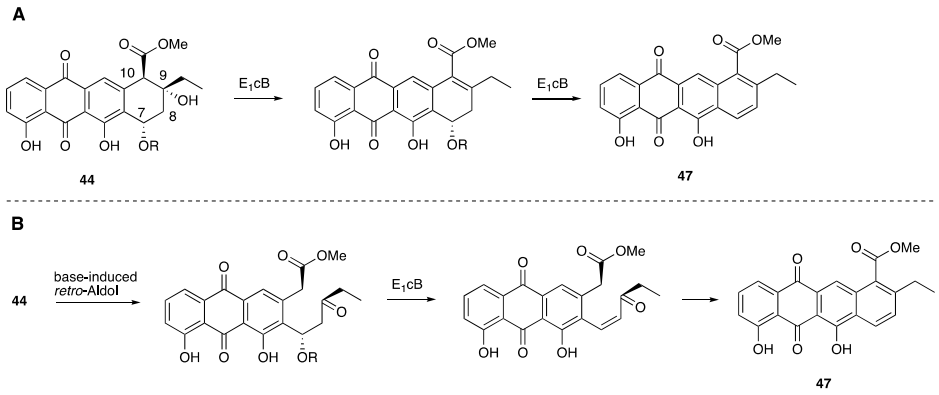
A mixture of disaccharide acceptor **40** and benzoyl-protected rhodinoside **30α** was subjected to IDCP to yield trisaccharide **41** in good yield and excellent α-selectivity. Deacylation of the benzoate in **41** and Dess-Martin oxidation of the resulting alcohol gave **42** near quantitatively. Treatment of **42** with ceric ammonium nitrate as the oxidant resulted in removal of both the anomeric *p*-methoxyphenyl protective group and the 3'-PMB group. DDQ removed solely the PMB group but left the anomeric phenolate intact. Gratifyingly, the silver(II)-mediated reaction conditions described in Chapter 2 were able to effect the orthogonal deprotection of the PMP group when a stoichiometric amount of the oxidant was used (more than 2 equivalents of $Ag(DPAH)_2$ resulted in partial removal of the PMB group). A final condensation of the so-obtained hemi-acetal with carboxylic acid **43** (described in Chapter 2) under Steglich conditions, yielded donor trisaccharide **26** ready for use in glycosylation events using Yu's gold-mediated glycosylation method.[20]

The synthesis of aklavinone (**27**), the acceptor chosen for the assembly of **10**, has been reported by several groups following the discovery of aclarubicin (**12**), both in racemic and enantiopure fashion.[21–27] More conveniently, acidic hydrolysis of aclarubicin (**12**) provides aglycon acceptor **27** quantitatively.[28] This set the stage for the key glycosylation envisaged, as shown in Scheme 6. Subjection of trisaccharide donor **26** and aklavinone (**27**) to a catalytic amount of PPh_3AuNTf_2 at -20 °C gave the desired trisaccharide **44** in 85% yield.



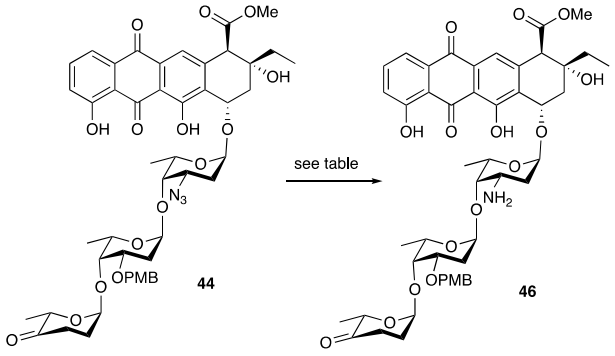
Scheme 6. Glycosylation of trisaccharide donor **26** to aklavinone **27** and ensuing attempted deprotections. *Reagents and conditions:* (a) PPh_3AuNTf_2 (10 mol%), 4 Å MS, DCM, 85% (8:1 α:β); (b) DDQ, DCM/pH 7 phosphate buffer (18:1, v/v), quant.

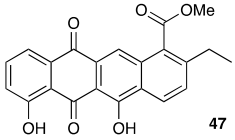
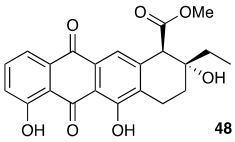
The stereoselectivity of the reaction was good (8:1 α:β), and the α-glycoside could be obtained in pure form by silica gel column chromatography. Removal of the PMB-ether was achieved using a large excess of DDQ in a biphasic, phosphate buffered system to yield the corresponding alcohol **45** quantitatively. Final azide deprotection however proved troublesome. Table 1 depicts the results from attempts at the reduction of the azide present in **44** into the desired amine, using phosphines, thiolates, hydrogenation and tin-hydride reagents. The Staudinger conditions as used in Chapter 2 (PPh_3, THF/H_2O) led to the formation of bisanhydroaklavinone **47**. This product has also been described in literature,[29,30] and has been referred in literature to as aclacinomycin F.[31] Two mechanistic explanations for the formation of **47** in the attempted azide reduction of **44** are given in Scheme 7.



Scheme 7. *Retro*-aldol / E_1cB pathway giving rise to fully aromatized aklavinone **47**.

Table 1. Azide-deprotecting conditions attempted on **44**.

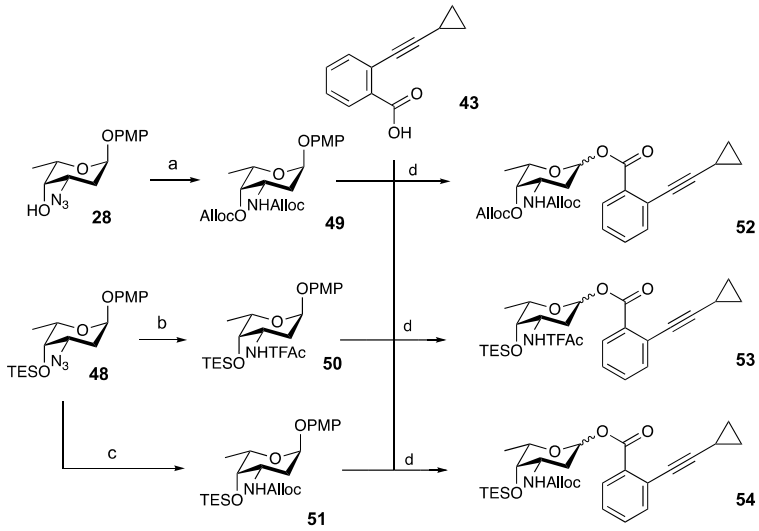


Entry	Deprotection conditions	Observed product(s)
1	PPh_3, THF/H_2O, 50 °C	 **47**
2	H_2S, THF/pyr.	**47**
3	1,3-propanedithiol, Et_3N, DMF	**47**
4	PtO_2, morpholine, H_2, THF	 **48**
5	PMe_3, THF/H_2O	Complex mixture
6	Lindlar's catalyst, MeOH	Complex mixture
7	Zn/NH_4Cl, MeOH/H_2O	Complex mixture
8	$Sn(SPh)_3HEt_3N$, THF	Complex mixture
9	Bu_2SnH_2	No conversion

E_1cB elimination, facilitated by the relatively acidic proton at C-10, would result in *net* dehydration over C-9 and C-10. This results in increased acidity of the C-8 protons, giving again a good E_1cB substrate, releasing the glycoside and resulting in fully aromatized **47**. Alternatively, the β-hydroxy ester might be able to undergo *retro*-aldol reaction to yield the corresponding keto-esters under basic condition. Base-induced elimination of the glycoside on C-7 in an E_1cB fashion is then facilitated by the newly

formed double bond being conjugated to the anthraquinone moiety. Then, aldol condensation closes the D-ring again, with a final dehydration process facilitated by full aromatization of this ring to also yield **47**. Subjection of **44** to a thiolate-based azide reduction (entries 2 and 3) resulted in the same degradation product. Hydrogenation of the azide was attempted using Adam's catalyst (PtO_2), which is known to be able to reduce azides whilst leaving benzyl groups intact.[32,33] Unfortunately cleavage of the benzylic trisaccharide could not be prevented, even when poisoning this catalyst with morpholine. Other procedures evaluated include the use of trimethylphosphine, Lindlar's catalyst (palladium on calcium carbonate), Zn/NH_4Cl, $Sn(SPh)_3HEt_3N$[34] and dibutyltin dihydride,[35] but all these reactions led to complex mixtures.

As the azide reduction required for the preparation of aklavinone-trisaccharide **10** proved very troublesome, other amine protecting groups were investigated, in the first instance for the preparation of monosaccharidic anthracyclines **2** and **4**.

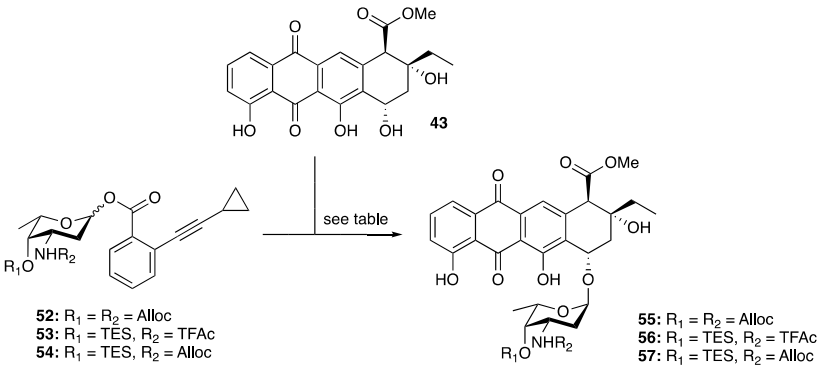


Scheme 8. Preparation of L-daunosamine *ortho*-alkynylbenzoate donors **52**-**54**. *Reagents and conditions:* (a) *i*. polymer-bound PPh_3, THF, H_2O; *ii.* allylchloroformate, pyr., DCM, -20 °C, 42% over 2 steps; (b) *i.* PPh_3, THF, H_2O; *ii.* trifluoroacetic anhydride, Et_3N, DCM, 91% over 2 steps; (c) polymer-bound PPh_3, THF, H_2O; *ii.* allylchloroformate, pyr., DCM, -20 °C, 88% over 2 steps; (d) *i.* Ag(II)(hydrogen dipicolinate)$_2$, NaOAc, MeCN, H_2O, 0 °C; *ii.* EDCI·HCl, DIPEA, DMAP, DCM, 98% over 2 steps for **51** (1:20 α:β), 66% over 2 steps for **52** (1:4 α:β), 73% over 2 steps for **53** (β only).

Protected L-daunosamine **28** (Chapter 2) was subjected to Staudinger reduction of the azide, followed by Alloc protection of both the amine and the hydroxyl group to yield **49**. Staudinger reduction of 4-silylated **48** (Chapter 2), followed by *N*-acylation with

either trifluoroacetic anhydride or allyl chloroformate yielded **50** and **51**, respectively. Conversion of *p*-methoxyphenyl acetals **49**-**51** proceeded analogously to the preparation of trisaccharide donor **26** in Scheme 4 to give *ortho*-alkynylbenzoates **52**-**54** in good yields.

Table 2. Glycosylation of *ortho*-alkynylbenzoates **52**-**54** to aklavinone **27**.



Reagents and conditions: (a) 2 eq of. **27**, PPh_3AuNTf_2 (10 mol%), 4 Å MS, T, 0.05M in DCM.

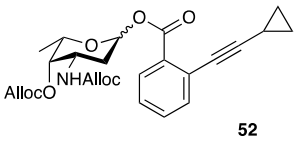
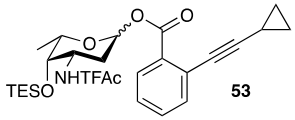
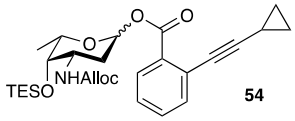
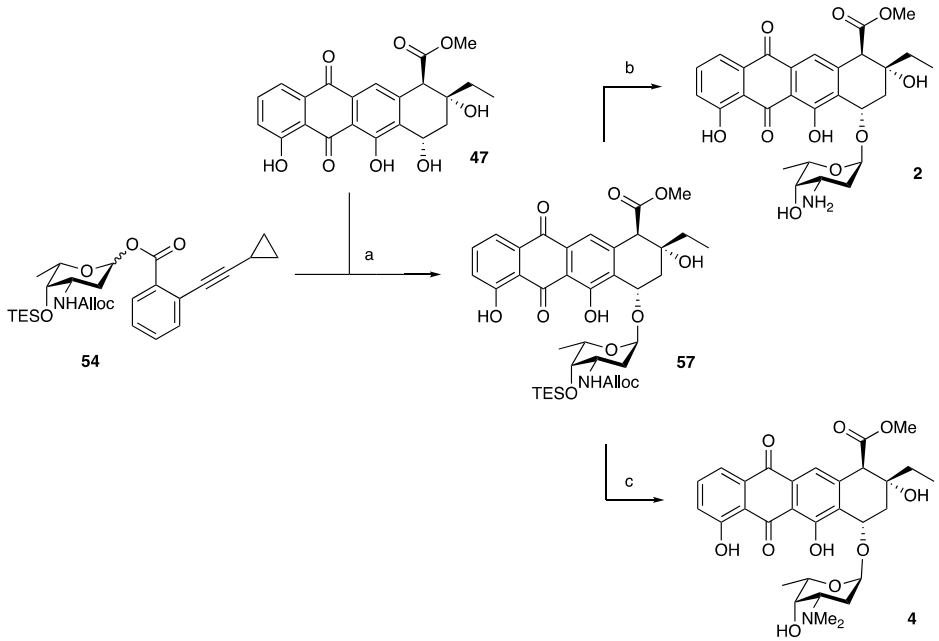
Entry	Donor	Temperature	Yield (α:β ratio).
1	 **52**	RT	58% (6.6:1 α:β)
2	-	-20 °C	93% (6.7:1 α:β)
3	-	-78 °C to RT	87% (6.3:1 α:β)
4	 **53**	RT	59% (>20:1 α:β)
5	 **54**	-20 °C	73% (>20:1 α:β)

Table 2 shows the glycosylation of *ortho*-alkynylbenzoates **52**-**54** to aklavinone **27** under PPh_3AuNTf_2 catalysis, towards the synthesis of **2** and **4**. The first three entries show the influence of temperature on the reaction outcome using donor **52**. All three reactions, performed at different temperatures (RT, -20 °C and -78 °C to -20 °C) gave a similar outcome in terms of stereoselectivtity (α/β = 6.3-6.7:1) providing inseparable

anomeric mixtures of **55**. The flexible 4-*O*-Alloc group may not be able to block the bottom-face of the ring as well as the bulky silyl ether, in the analogous building block, used in Chapter 2. By lowering the reaction temperature from RT to -20 °C, the yield of the glycosylation was significantly improved. Entries 4 and 5 show that *N*-trifluoroacetate and *N*-allyloxycarbamate protected donors **53** and **54** both provide

stereoselective glycosylations to yield **56** and **57**, respectively. Upon treatment of **55** with $Pd(PPh_3)_4$ and Me_2NTMS/TMSOAc as allyl-scavenger system,[36] **2** was obtained as a still inseparable anomeric mixture. Desilylation of **56** proceeded uneventfully but attempts at removal of the trifluoroacetamide (excess NaOMe, MeOH[22]) resulted in degradation of the aglycone moiety, as previously shown in Scheme 7.

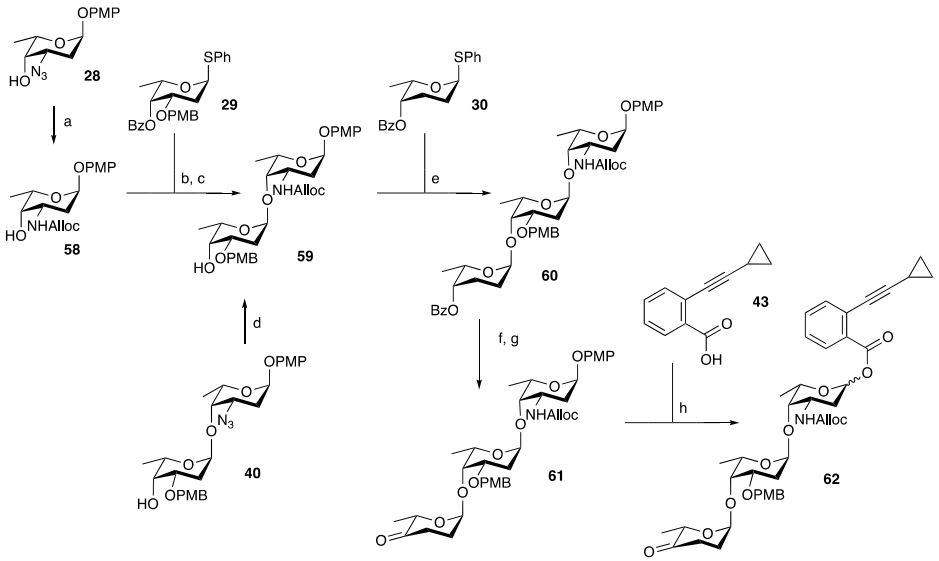


Scheme 9. Synthesis of aklavinone-monosaccharides **2** and **4**. *Reagents and conditions:* (a) PPh_3AuNTf_2 (10 mol%), DCM, -20 °C, 73% (>20:1 α:β); (b) *i.* $Pd(PPh_3)_4$, NDMBA, DCM; *ii.* HF·pyridine, pyr., 40% over 2 steps; (c) *i.* $Pd(PPh_3)_4$, NDMBA, DCM; *ii.* aq. CH_2O, $NaBH(OAc)_3$, EtOH; *iii.* HF·pyridine, pyr., 43% over 3 steps.

Palladium-catalyzed removal of the *N*-Alloc group in **57** was performed using a catalytic amount of $Pd(PPh_3)_4$ and *N,N*-dimethylbarbituric acid (NDMBA) as the allyl-scavenger,[37] as shown in Scheme 9. The use of the Me_2NTMS-TMSOAc-$Pd(PPh_3)_4$ system[36,37] was found to be inferior, as it often led to prolonged reaction times and significant formation of *N*-allylated products. This was followed by desilylation using HF·pyr complex to give known monosaccharide **2** in decent yield over 2 steps.[38]

The corresponding dimethylamine **4** could be prepared by the same removal of the Alloc group, followed by reductive alkylation to formaldehyde using $NaBH(OAc)_3$ and a final desilylation. The spectral data of **4** is in agreement with that described in the literature.[39]

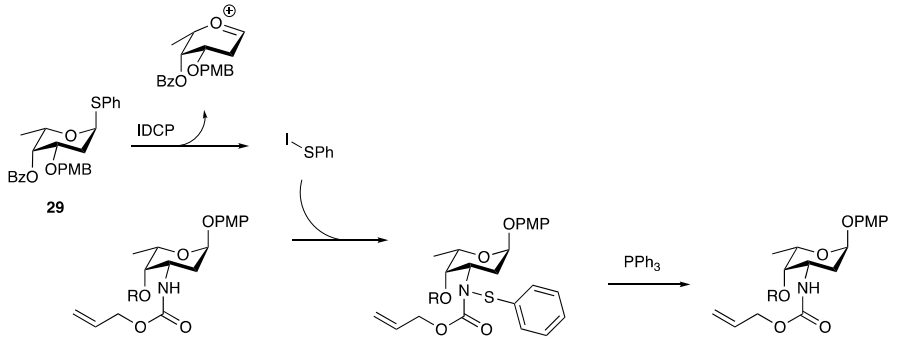
With the lessons learned from the synthesis of **2** and **4**, it was decided to switch the strategy for the preparation of the envisaged aklavinone trisaccharides to include the use of an Alloc carbamate as the amine protecting group, as shown for the synthesis of **10** in Scheme 10.



Scheme 10. Preparation of the *N*-allyloxycarbonyl protected trisaccharide donor **62**. *Reagents and conditions:* (a) polymer-bound PPh_3, THF, H_2O, then Alloc-OSu, $NaHCO_3$, 89%; (b) IDCP, Et_2O, DCE (4:1 v/v), then PPh_3, 90%; (c) NaOMe, MeOH, 90%; (d) polymer-bound PPh_3, THF, H_2O, then Alloc-OSu, $NaHCO_3$, 95%; (e) IDCP, Et_2O, DCE (4:1 v/v), then PPh_3, quant.; (f) NaOMe, MeOH, 85%; (g) Dess-Martin periodinane, $NaHCO_3$, DCM, 97%; (h) *i.* Ag(II)(hydrogen dipicolinate)$_2$, NaOAc, MeCN, H_2O, 0 °C; *ii.* EDCI·HCl, DIPEA, DMAP, DCM, 75% over 2 steps (1:7 α:β).

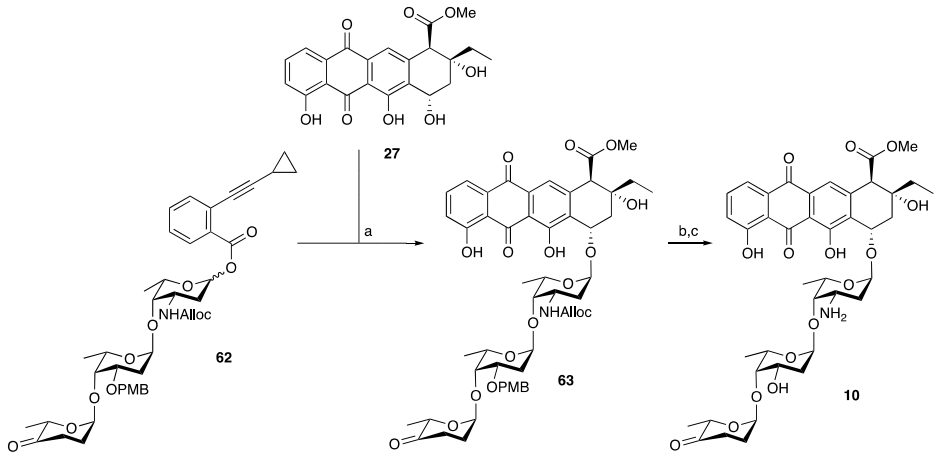
Azide acceptor **28** could easily be transformed into its Alloc counterpart **58** by treatment with triphenylphosphine in wet THF, followed by addition of *N*-allyloxycarbonylsuccinimide. Treatment of thioglycoside **29** and acceptor **58** with IDCP, as described in Scheme 4, gave the resulting disaccharide **59** in excellent yield and anomeric ratio after debenzoylation. During the course of the IDCP-glycosylation, it was observed that the released phenylthio-iodide was captured by the *N*-allyloxycarbamate moiety present in the acceptor.[17,40] As depicted in Scheme 11, addition of triphenylphosphine after the glycosylation to the resultant sulfenamide

cleaved the undesired N-S bond with release of phenylthio-(triphenylphosphonium) iodide and returned the carbamate function. This phenomenon can also occur in the preactivation of thioglycosides with the Tf_2O-diphenylsulfoxide promotor system when a carboxybenzyl-protected amine was present.[41]



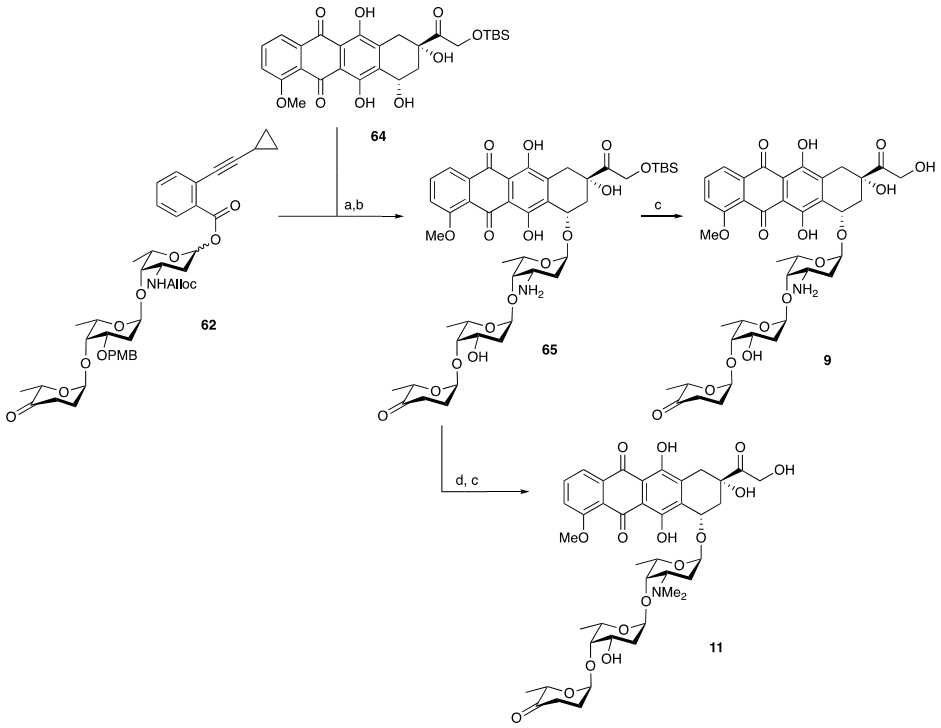
Scheme 11. Sulfenamide formation during IDCP-mediated glycosylation of *N*-Alloc-containing glycosides, and return of the carbamate upon addition of PPh_3.

Alloc-protected disaccharide **59** could also be prepared from 3-azide disaccharide **40** using the same procedure emplyed for the conversion of acceptor **28** to **58**. In the next glycosylation event, the addition of IDCP to the mixture of disaccharide acceptor **59** and thioglycoside **30** furnished trisaccharide **60** quantitatively. Deacylation of the C-4‴-benzoate, followed by Dess-Martin oxidation of the resulting alcohol gave cineruloside trisaccharide **61**. Conversion to the *ortho*-alkynylbenzoate proceeded analogously to the preparation of **26** in Scheme 4 to give *N*-Alloc protected trisaccharide donor **62**.



Scheme 12. Synthesis of aklavinone-trisaccharide **10**. Reagents and conditions: (a) PPh_3AuNTf_2 (10 mol%), DCM, -20°C, 71%; (b) DDQ, DCM/pH 7 phosphate buffer (18:1, v/v), 90%; (c) $Pd(PPh_3)_4$, NDMBA, DCM, 61%.

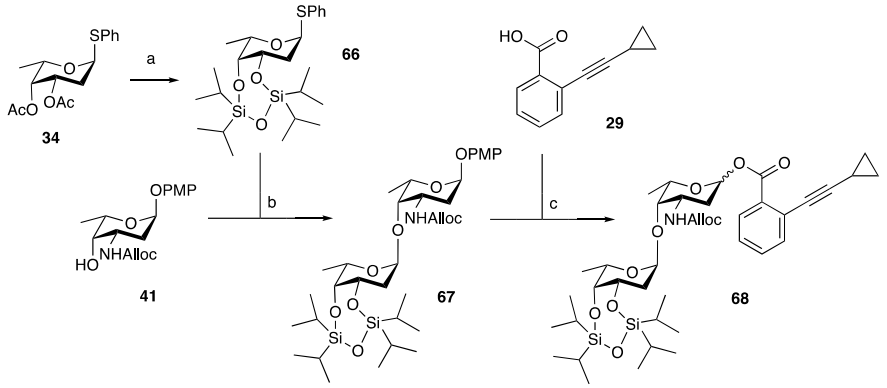
Subjection of a mixture of donor **62** and aklavinone **27** to Yu's conditions (10 mol% PPh_3AuNTf_2) at -20 °C gave the protected trisaccharide anthracycline with complete α-selectivity. DDQ-oxidation of the PMB group (in DCM and pH 7 phosphate buffer) proceeded uneventfully to give **63** and leave only the Alloc group for the final deprotection. The amine was liberated using the Pd/NMDBA system to give trisaccharide amine **10**, whose spectral data was in perfect agreement with literature precedent.[42]



Scheme 13. Synthesis of doxorubicinone-trisaccharides **9** and **11**. *Reagents and conditions:* (a) *i.* PPh_3AuNTf_2 (10 mol%), DCM; *ii.* DDQ, DCM, pH 7 phosphate buffer (18:1, v/v), 57% over 2 steps; (b) $Pd(PPh_3)_4$, NDMBA, DCM, 81%; (c) HF·pyridine, pyr., 73% for **9**, 73% for **11**; (d) aq. CH_2O, $NaBH(OAc)_3$, EtOH, 52%.

Attention was next focused on the synthesis of doxorubicinone-derived trisaccharides **9** and **11**, as depicted in Scheme 13. Subjecting *N*-allyloxycarbonyl protected trisaccharide donor **62** and an excess of 14-*O*-TBS-doxorubicinone **64** (described in Chapter 2) to catalytic PPh_3AuNTf_2 gave the desired trisaccharide **65** with excellent α-selectivity after oxidative removal of the PMB group (DDQ) and the Alloc group. The use of the azide-containing donor **26** was also able to give the corresponding protected doxorubicinone trisaccharide in excellent yield and α-selectivity, but the azide deprotection yielded complex mixtures (see the Experimental section for details).

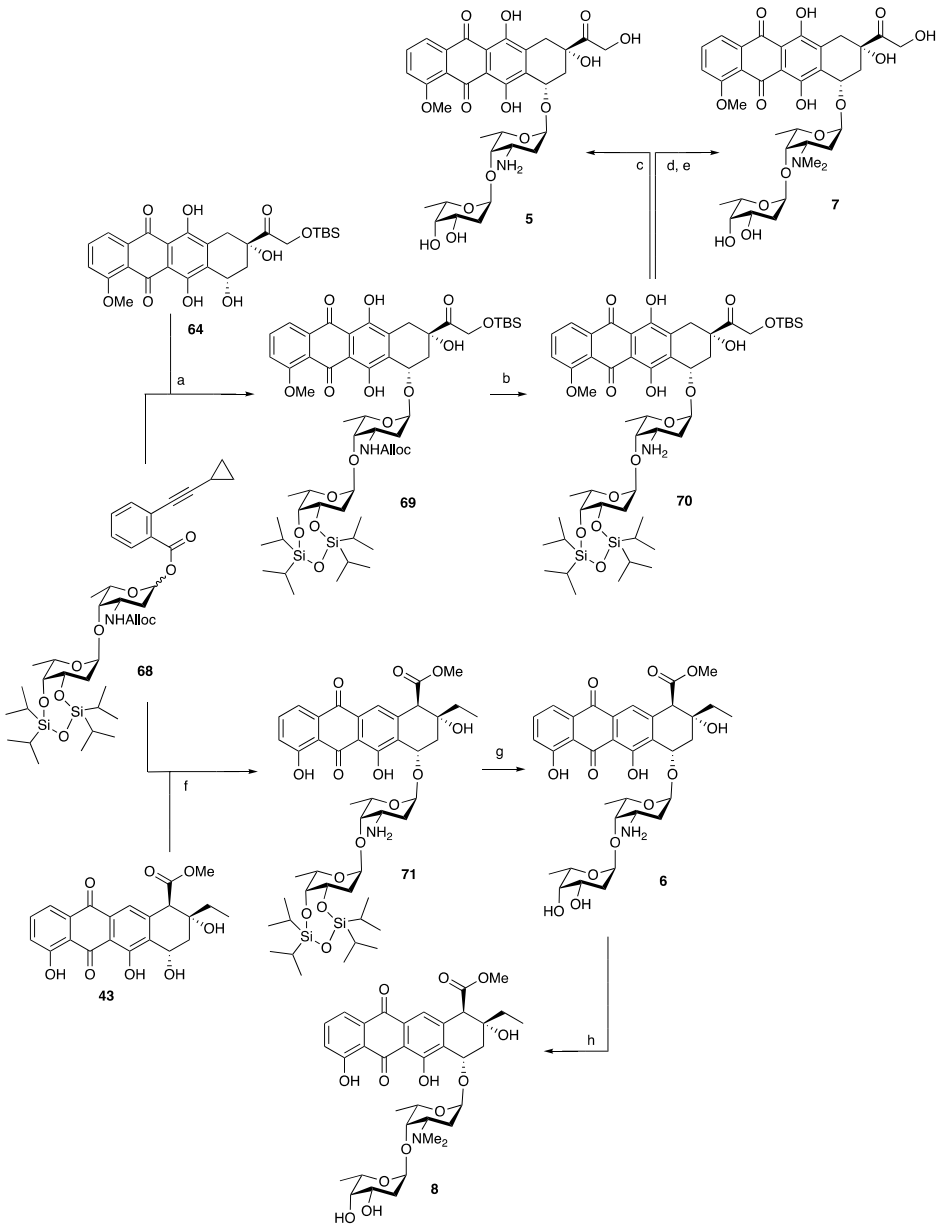
Treatment with Olah's reagent (HF·pyridine complex) finally gave trisaccharide amine **9**. The corresponding dimethylamine **11** was obtained from the reductive alkylation of formaldehyde and amine **65**, followed by desilylation. The obtained spectral data matched those described in the literature.[11]



Scheme 14. Synthesis of disaccharide *ortho*-alkynylbenzoate donor **68**.
Reagents and conditions: (a) *i.* NaOMe, MeOH; *ii.* tetraisopropyldisiloxane dichloride, pyr., 67% over 2 steps; (b) IDCP, Et_2O, DCE (4:1 v/v), then PPh_3, 89%; (c) *i.* Ag(II)(hydrogen dipicolinate)$_2$, NaOAc, MeCN, H_2O, 0 °C; *ii.* EDCI·HCl, DIPEA, DMAP, DCM, 84% over 2 steps (1:8 α:β).

In the preparation of anthracycline disaccharides **5**-**8**, the terminal diol was protected as its tetraisopropyldisiloxyl ether, as the previous and this Chapter has shown that silyl ethers can be readily removed from anthraquinone glycosides. The steric bulk of this protecting group should allow for effective blocking of the *beta*-face of the donor to facilitate the α-selective preparation of the disaccharide. Thus, L-olioside **66** was prepared as depicted in Scheme 14 from acetate **34** by removal of the acetyl esters and treatment of the resulting diol with tetraisopropyldisiloxane dichloride. A mixture of this thioglycoside and acceptor **41** was subjected to IDCP to give the desired disaccharide **67** in excellent yield and stereoselectivity. The disaccharide was converted to the corresponding Yu donor with the oxidation-Steglich esterification sequence as described earlier in this Chapter to give **68**.

The preparation of disaccharide donor **68** set the stage for coupling to the two aglycone acceptors **64** and **43** as outlined in Scheme 15. Treatment of a mixture of donor **68** and acceptor **64** with PPh_3AuNTf_2 proceeded stereoselectively to give **69**. Ensuing Alloc removal proceeded quantitatively to give **70**, after which HF·pyridine-mediated desilylation yielded 4'-oliosyl-doxorubicin **5**. Subjecting amine **70** to reductive alkylation (aq. CH_2O, $NaBH(OAc)_3$) followed by desilylation resulted in dimethylated **7**.



Scheme 15. Synthesis of anthraquinone disaccharides **5**-**8**. *Reagents and conditions:* (a) PPh_3AuNTf_2 (10 mol%), DCM, 64%; (b) $Pd(PPh_3)_4$, NDMBA, DCM, quant.; (c) HF·pyridine, pyr., 76%; (d) aq. CH_2O, $NaBH(OAc)_3$, EtOH, 71%; (e) HF·pyridine, pyr., 81%; (f) *i.* PPh_3AuNTf_2 (10 mol%), -20 °C, DCM; *ii.* $Pd(PPh_3)_4$, NDMBA, DCM, 87% over 2 steps; (g) HF·pyridine, pyr., 41%; (h) aq. CH_2O, $NaBH(OAc)_3$, EtOH, 34%.

Subjection of donor **68** and aklavinone **27** to gold(I)-mediated glycosylation proceeded stereoselectively, followed by removal of the Alloc group to give **71**. Final removal of the disiloxane moiety (HF·pyridine) gave disaccharide **6**. Double reductive methylation of the amine in **71** was followed by desilylation. Unfortunately, the HF·pyridine mediated desilylation was accompanied by loss of methyl groups of the amine. This *N*-demethylation was not observed in the preparation of **7**. It is known that the dihydroxyanthraquinone moiety in this compound is a powerful redox mediator, which might have effected this degradation.[47] Therefore, the double reductive *N*-methylation was performed on fully deprotected **6** to give the desired disaccharide **7** in acceptable yield, and with spectral data in agreement with literature precedent.[43]

Conclusions

The reasons behind the different biological activity profiles of doxorubicin and aclarubicin remain poorly understood. The preparation of hybrid structures filling the chemical space between these two natural compounds should aid in understanding these differences, with possible implications for the design of new anthracyclines for use in the clinic. This Chapter describes the synthesis of two monosaccharides (**3** and **4**), 4 disaccharides (**5**-**8**) and 3 trisaccharides (**9**-**11**), differing in *N*-methylation pattern and aglycon. The compounds **2**[38], **3**[44], **4**[39], **8**[43], **10**[42] and **11**[11] have been reported before, whereas **5**, **6**, **7** and **9** are new. The assembly of the compounds reported here relied on the use of Yu's *ortho*-alkynylbenzoate glycosylation method, which uses catalytic amounts of gold(I) to activate glycosyl donors. The relevant di- and trisaccharide donors were assembled by (iterative) stereoselective IDCP-mediated thioglycosylation, and the anthracycline aglycones were obtained from acidic hydrolysis of the parent anthracyclines. The library of doxorubicin/aclarubicin hybrids **1** – **12** should aid in establishing a proper structure-activity relationship to explain the different biological activities of these two drugs. The chemistry disclosed here should be amenable for the generation of a wider variety of anthracyclines.

Experimental procedures and characterization data

All reagents were of commercial grade and used as received. Traces of water from reagents were removed by co-evaporation with toluene in reactions that required anhydrous conditions. All moisture/oxygen sensitive reactions were performed under an argon atmosphere. DCM used in the glycosylation reactions was dried with flamed 4Å molecular sieves before being used. Reactions were monitored by TLC analysis with detection by UV (254 nm) and where applicable by spraying with 20% sulfuric acid in EtOH or with a solution of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4\cdot 2H_2O$ (10 g/L) in 10% sulfuric acid (aq.) followed by charring at ~150 °C. Flash column chromatography was performed on silica gel (40-63μm). ^1H and ^{13}C spectra were recorded on a Bruker AV 400 and Bruker AV 500 in $CDCl_3$, CD_3OD, pyridine-d5 or D_2O. Chemical shifts (δ) are given in ppm relative to tetramethylsilane (TMS) as internal standard (^1H NMR in $CDCl_3$) or the residual signal of the deuterated solvent. Coupling constants (J) are given in Hz. All ^{13}C spectra are proton decoupled. Column chromatography was carried out using silica gel (0.040-0.063 mm). Size-exclusion chromatography was carried out using Sephadex LH-20, using DCM:MeOH (1:1, v/v) as the eluent. Neutral silica was prepared by stirring regular silica gel in aqueous ammonia, followed by filtration, washing with water and heating at 150°C overnight. High-resolution mass spectrometry (HRMS) analysis was performed with a LTQ Orbitrap mass spectrometer (Thermo Finnigan), equipped with an electronspray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10 mL/min, capillary temperature 250 °C) with resolution R = 60000 at m/z 400 (mass range m/z = 150 – 2000) and dioctyl phthalate (m/z = 391.28428) as a "lock mass", or with a Synapt G2-Si (Waters), equipped with an electronspray ion source in positive mode (ESI-TOF), injection via NanoEquity system (Waters), with LeuEnk (m/z = 556.2771) as "lock mass". Eluents used: MeCN:H_2O (1:1 v/v) supplemented with 0.1% formic acid. The high-resolution mass spectrometers were calibrated prior to measurements with a calibration mixture (Thermo Finnigan).

General procedure A: *p*-Methoxyphenolate oxidative deprotection

To a solution of the *p*-methoxyphenyl glycoside in 1:1 MeCN:H_2O (0.02M, v/v) were added NaOAc (10 eq) and then $Ag(DPAH)_2\cdot H_2O$ (2.1 eq for trisaccharides, 4 eq for monosaccharides) portionwise over 30 minutes at 0°C. The mixture was stirred until disappearance of the starting material; after which it was poured into sat. aq. $NaHCO_3$. This was then extracted with DCM thrice, dried over $MgSO_4$ and concentrated *in vacuo* gave the crude lactols.

General procedure B: Alkynylbenzoate esterification

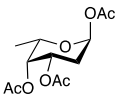
A solution of *ortho*-cyclopropylethynylbenzoic acid methyl ester (for preparation, see Chapter 2) in THF (5 mL/mmol) and 1M NaOH (5 mL/mmol) was stirred at 50 °C for at least 5 hours. It was then poured into 1M HCl (6 mL/mmol) and extracted with DCM thrice. The combined organic layers were then dried over $MgSO_4$ and concentrated *in vacuo*. The resultant acid **43** was then used without further purification.

To a solution of the above crude lactol in DCM (0.1M) were added DIPEA (9 eq), DMAP (1 eq), EDCI·HCl (3.2 eq) and the above carboxylic acid **43** (3 eq). After stirring overnight, the mixture was diluted with DCM and washed with sat. aq. $NaHCO_3$ and brine. Drying over $MgSO_4$, concentration *in vacuo* and column chromatography of the residue (EtOAc:pentane) gave the title alkynylbenzoates.

General procedure C: Au(I)-catalysed glycosylation

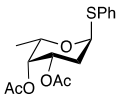
To a solution of the glycosyl donor and the required anthracycline acceptor (1-2 eq) in DCM (0.05M mL), activated molecular sieves (4Å) were added. The mixture was stirred for 30 minutes. Subsequently, a freshly prepared 0.1M DCM solution of PPh_3AuNTf_2 (prepared by stirring 1:1 PPh_3AuCl and $AgNTf_2$ in DCM for 30 minutes) (0.1 eq) in DCM was added dropwise at the designated temperature. After stirring 30 minutes (for RT) or overnight (-20°C or lower), the mixture was filtered and concentrated *in vacuo*. Column chromatography (EtOAc:pentane or Et_2O:pentane and then acetone:toluene) followed by (if required) size-exclusion chromatography (Sephadex LH-20, 1:1 DCM:MeOH v/v) gave the title glycosides.

1,3,4-Tri-*O*-acetyl-2-deoxy-α-L-fucopyranoside (32)[13]



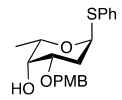
Commercially available L-fucose **31** (7.42 g, 45.2 mmol) was dissolved in pyridine (80 mL) and acetic anhydride (65 mL) and heated to 100 °C. After stirring for 1.5 hours, the resulting solution was concentrated *in vacuo* and additionally coevaporated twice with toluene to afford crude tetraacetyl-L-fucose as a viscous orange oil. The latter was then dissolved in DCM (40 mL), whereupon hydrobromic acid (33 wt. % HBr in AcOH, 40 mL) was added dropwise. After stirring overnight at ambient temperature, the resulting solution was poured onto a stirring suspension of Na_2CO_3 (40.0 g) in DCM (1 L) and left to stir for 1 hour, after which the suspension was filtered and subjected to the aforementioned work-up once more. The resulting solution was then concentrated *in vacuo* to afford the crude fucosyl bromide as an orange oil. This was then dissolved in toluene (1.5 L) in a two-necked 2L round-bottom flask. After the addition of azobisisobutyronitrile (742 mg, 4.52 mmol, 0.10 eq), it was stirred at 80 °C for 30 minutes, whereupon a solution of tributyltin hydride (18.2 mL, 58.0 mmol, 1.3 eq) was added *via* a syringe pump over the duration of 16 hours at the aforementioned temperature. Stirring of the resulting solution commenced for a further 2 hours and was subsequently concentrated *in vacuo*. Purification by column chromatography (20:80 – 40:60 EtOAc:pentane) afforded a mixture of the title compound and its 1-deoxy regioisomer **20** (11.08 g, containing 30.3 mmol desired product, 67% over 3 steps) as a white solid. Crystallisation from hot EtOH yielded the pure title compound (5.93 g, 21.6 mmol, 48% over 3 steps). Spectral data of the title compound was in accordance with that of literary precedence.[13]

Phenyl 2-deoxy-3,4-di-*O*-acetyl-thio-α-L-fucopyranoside (34)[13]



To a solution **32** (5.92 g, 21.6 mmol) in DCM (220 mL) at -78 °C, were added thiophenol (2.3 mL, 22.5 mmol, 1.04 eq) and $BF_3{\cdot}OEt_2$ (7.5 mL, 54 mmol, 2.5 eq) dropwise consecutively. The resulting solution was stirred at that temperature for 2 hours, after which it was slowly warmed up to -20 °C. It was then quenched by addition of Et_3N and concentrated *in vacuo*. Column chromatography (20:80 EtOAc:pentane) gave a residu which was dissolved in EtOAc, washed with sat. aq. $NaHCO_3$ twice and concentrated *in vacuo* to give the title compound as a white solid (7.00 g, 21.6 mmol, quant., 10:1 α:β). Spectral data of the major α-anomer was in accordance with that of literary precedence.[13]

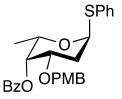
Phenyl 2-deoxy-3-*O*-*p*-methoxybenzyl-thio-α-L-fucopyranoside (35)[13]



A solution of **34** (1.62 g, 5.00 mmol) and NaOMe (cat. amount) in MeOH (100 mL) was stirred overnight. It was then quenched by addition of Amberlite IR120 (H^+ form), filtered and concentrated *in vacuo* to give the intermediate diol.

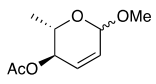
This diol was suspended in toluene (80 mL) and after the addition of dibutyltin oxide (1.25 g, 5.00 mmol, 1 eq), was heated to reflux in a Dean-Stark apparatus overnight. Thereafter, tetra-*n*-butylammonium bromide (3.22 g, 10.0 mmol, 2 eq) and 4-methoxybenzyl chloride (2.03 mL, 15.0 mmol, 3 eq) were added consecutively and stirring commenced overnight at 90 °C. Hereafter, the resulting solution was concentrated *in vacuo* and purification by column chromatography (5:95 – 20:80 EtOAc:pentane) afforded the title compound as a yellow wax (1.73 g, 4.80 mmol, 96% over 2 steps, 10:1 α:β). Spectral data of the major α-anomer was in accordance with that of literary precedence.[13]

Phenyl 4-*O*-benzoyl-2-deoxy-1-thio-α-L-fucopyranoside (29)



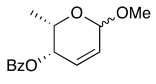
To a solution of **35** (10.7 g, 29.8 mmol) in pyridine (150 mL) and DCM (30 mL) was added benzoyl chloride (11.3 mL, 89.4 mmol, 3 eq). After stirring overnight, MeOH was added to quench and the mixture was concentrated *in vacuo*. Column chromatography (4:96 – 5:95 EtOAc:pentane) gave the title compound as a light yellow solid (11.3 g, 24.3 mmol, 82%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.22 – 8.07 (m, 2H), 7.63 – 7.51 (m, 1H), 7.51 – 7.35 (m, 4H), 7.35 – 7.17 (m, 5H), 6.89 – 6.77 (m, 2H), 5.80 (d, *J* = 5.6 Hz, 1H), 5.62 (d, *J* = 2.9 Hz, 1H), 4.73 (d, *J* = 11.0 Hz, 1H), 4.57 (q, *J* = 6.6 Hz, 1H), 4.43 (d, *J* = 11.0 Hz, 1H), 4.01 (ddd, *J* = 12.3, 4.8, 2.9 Hz, 1H), 3.78 (s, 3H), 2.60 – 2.44 (m, 1H), 2.15 (ddt, *J* = 13.5, 4.9, 1.2 Hz, 1H), 1.22 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 133.2, 131.2, 130.0, 129.6, 129.1, 128.5, 127.3, 114.0, 84.6, 72.1, 70.1, 69.5, 66.4, 55.4, 32.6, 17.0. HRMS: $(M + Na)^+$ calculated for $C_{27}H_{28}O_5SNa$ 487.1555, found 487.1552.

Methyl 4-*O*-acetyl-2,3-dideoxy-α,β,-L-*erythro*-hex-2-enopyranoside (37)[14]



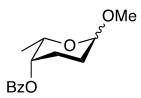
To a solution of L-rhamnal **36** (18.1 g, 84.6 mmol) in DCM (380 mL) and MeOH (7.2 mL, 178 mmol, 2.1 eq) was added tin(IV) chloride (1M $SnCl_4$ solution in DCM, 4.23 mL, 4.23 mmol, 0.05 eq) dropwise. After stirring for 40 minutes, the resulting solution was poured onto sat. aq. $NaHCO_3$ and the organic layer was washed with additional sat. aq. $NaHCO_3$. The combined aqueous layers were then extracted with DCM and the resulting combined organic layers were successively washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (20:80 EtOAc:pentane) afforded the title compound as a light brown oil (12.7 g, 68.0 mmol, 80%, 6:1 α:β). The material was carried on without further purification. Spectral data of the major α-anomer was in accordance with that of literary precedence.[14]

Methyl 4-*O*-benzoyl-2,3-dideoxy-α,β-L-*threo*-hex-2-enopyranoside (38)[16]



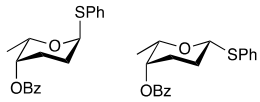
To a solution of **37** (12.7 g, 68.0 mmol, 6:1 α:β) in MeOH (85 mL) was added sodium methoxide (0.735 g, 13.6 mmol, 0.2 eq). After stirring for 1 hour, the resulting solution was neutralized by addition of acetic acid and then concentrated *in vacuo*. Purification by column chromatography (30:70 – 40:60 Et_2O:pentane) afforded the allylic alcohol as a yellow oil (8.04 g, 55.8 mmol, 82%, 6:1 α:β). This was then dissolved in THF (370 mL) and benzoic acid (10.2 g, 83.7 mmol, 1.5 eq) and triphenylphosphine (22.0 g, 83.7 mmol, 1.5 eq) were added consecutively. Subsequently, the solution was cooled to 0 °C, whereupon diethyl azodicarboxylate (13.8 mL, 86.5 mmol, 1.55 eq) was added dropwise. After stirring for 1.5 hours, the resulting solution was concentrated *in vacuo*, diluted with DCM and the organic layer successively washed twice with sat. aq. $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (5:95 – 10:90 EtOAc:pentane) afforded the title compound as a colourless oil (9.64 g, 38.8 mmol, 70%, 10:1 α:β). Spectral data of the major α-anomer was in accordance with that of literary precedence.[16]

Methyl 4-*O*-benzoyl-2,3-dideoxy-α-L-*threo*-hexopyranoside (39)



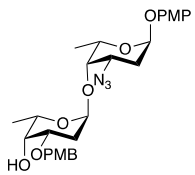
A solution of **38** (6.06 g, 24.4 mmol, 10:1 α:β) in MeOH (120 mL) was degassed with argon, whereupon palladium black (740 mg) was added, followed by the subsequent sparging of H_2(g) through the suspension. After stirring overnight, the resulting suspension was filtered over Celite and concentrated *in vacuo*. Purification by column chromatography (3:97 – 4:96 EtOAc:pentane) afforded the title compound as a colourless oil (5.56 g, 22.2 mmol, 91%, >16:1 α:β). Spectral data of the major α anomer was in accordance with that of literary precedence.[45]

Phenyl 4-*O*-benzoyl-2,3-dideoxy-1-thio-α,β-L-fucopyranoside (30α and 30β)



To a solution of **39** (3.05 g, 12.2 mmol) in DCM (60 mL) at -78°C were added thiophenol (1.30 mL, 12.7 mmol, 1.04 eq) and $BF_3{\cdot}OEt_2$ (3.75 mL, 30.5 mmol, 2.5 eq) dropwise. The mixture was allowed to warm up to -15°C over 4 hours, after which it was poured into sat. aq. $NaHCO_3$. The aqueous layer was extracted with DCM and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (2:98 – 10:90 EtOAc:pentane) gave the α-anomer and the β-anomers as clear oils (3.19 g, 9.71 mmol, 80%, α:β 1.2:1). Analytical data for the α-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.19 – 8.03 (m, 2H), 7.66 – 7.55 (m, 1H), 7.55 – 7.39 (m, 4H), 7.39 – 7.16 (m, 4H), 5.73 (d, *J* = 5.3 Hz, 1H), 5.13 (d, *J* = 3.4 Hz, 1H), 4.61 (qd, *J* = 6.6, 1.5 Hz, 1H), 2.44 (tt, *J* = 13.8, 5.1 Hz, 1H), 2.17 (tdd, *J* = 13.7, 4.4, 2.9 Hz, 1H), 2.13 – 2.00 (m, 1H), 1.87 (dt, *J* = 14.2, 3.5 Hz, 1H), 1.20 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.44, 133.25, 131.12, 129.86, 129.05, 128.59, 126.99, 84.98, 69.96, 66.35, 25.65, 24.77, 17.27. HRMS: $(M + Na)^+$ calculated for $C_{19}H_{20}O_3SNa$ 351.10254; found 351.10250.

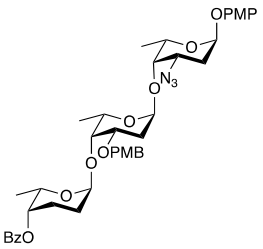
***p*-Methoxyphenyl-2-deoxy-3-O-*p*-methoxybenzyl-α-L-fucopyranosyl-(1→4)-3-azido-2,3-dideoxy-α-L-fucopyranoside (40)**



To a solution of the glycosyl acceptor **28** (1.54 g, 5.5 mmol, 1 eq) and the glycosyl donor **29** (3.58 g, 7.7 mmol, 1.4 eq) in 4:1 Et_2O:DCE (110 mL, v/v), activated molecular sieves (4Å) were added. The mixture was stirred for 30 minutes and then, at 10°C, iodonium dicollidinium perchlorate (10.3 g, 22.0 mmol, 4 eq) was added. After 4 hours, the mixture was diluted with Et_2O and filtered, washed with 10% aq. $Na_2S_2O_3$, 1M $CuSO_4$ solution twice, H_2O and then dried over $MgSO_4$. Concentration *in vacuo* and column chromatography (12:88 – 20:80 EtOAc:pentane) of the residue gave the crude

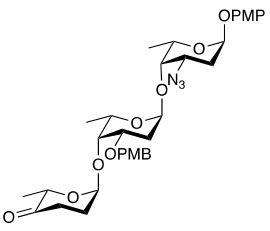
disaccharide. This was then dissolved in in MeOH (110 mL) and DCM (55 mL), after which NaOMe was added to pH=10. After stirring over 2 nights, it was neutralized by addition of Amberlite IR-120 (H^+ form), filtered and concentrated *in vacuo*. Column chromatography (30:70 – 50:50 EtOAc:pentane) gave the title compound as a thick yellow oil (2.51 g, 4.74 mmol, 85% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34 – 7.17 (m, 2H), 7.06 – 6.95 (m, 2H), 6.95 – 6.76 (m, 4H), 5.56 (d, *J* = 3.3 Hz, 1H), 5.05 (d, *J* = 3.7 Hz, 1H), 4.54 (q, *J* = 11.0 Hz, 2H), 4.33 (q, *J* = 6.6 Hz, 1H), 4.17 (ddd, *J* = 12.6, 4.7, 2.8 Hz, 1H), 4.01 (q, *J* = 6.6 Hz, 1H), 3.93 (ddd, *J* = 11.8, 5.1, 2.8 Hz, 1H), 3.84 (d, *J* = 2.9 Hz, 1H), 3.81 (s, 3H), 3.78 (d, *J* = 3.3 Hz, 4H), 2.18 – 1.95 (m, 5H), 1.34 (d, *J* = 6.5 Hz, 3H), 1.20 (d, *J* = 6.5 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 190.6, 159.5, 154.9, 150.8, 130.2, 129.5, 117.6, 114.7, 114.1, 99.6, 96.3, 75.1, 73.0, 70.0, 68.4, 67.6, 66.7, 56.9, 55.8, 55.4, 30.1, 29.9, 17.6, 17.1. HRMS: $(M + Na)^+$ calculated for $C_{27}H_{35}N_3O_8Na$ 552.2322; found 552.2326.

***p*-Methoxyphenyl-4-O-benzoyl-2,3-dideoxy-α-L-fucopyranosyl-(1→4)-2-deoxy-3-O-*p*-methoxybenzyl-α-L-fucopyranosyl-(1→4)-3-azido-2,3-dideoxy-α-L-fucopyranoside (41)**



To a solution of the glycosyl acceptor **40** (1.07 g, 2.00 mmol) and the glycosyl donor **30α** (877 mg, 2.67 mmol, 1.34 eq) in 4:1 Et_2O:DCE (41 mL, v/v), activated molecular sieves (4Å) were added. The mixture was stirred for 30 minutes and then, at 10°C, iodonium dicollidine perchlorate (3.75 g, 8.00 mmol, 4 eq) was added. After 75 minutes, the mixture was diluted with Et_2O and filtered, washed with 10% aq. $Na_2S_2O_3$, 1M $CuSO_4$ solution twice, H_2O and then dried over $MgSO_4$. Concentration *in vacuo* and column chromatography (10:90 – 30:70 EtOAc:pentane) of the residue gave the title compound as a fluffy white solid (1.38 g, 1.85 mmol, 92%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.12 – 8.04 (m, 2H), 7.64 – 7.50 (m, 1H), 7.50 – 7.38 (m, 2H), 7.31 – 7.22 (m, 4H), 7.05 – 6.92 (m, 2H), 6.92 – 6.76 (m, 4H), 5.55 (d, *J* = 2.5 Hz, 1H), 5.10 (d, *J* = 3.6 Hz, 1H), 5.05 (s, 1H), 4.98 (s, 1H), 4.68 (d, *J* = 11.7 Hz, 1H), 4.60 – 4.50 (m, 2H), 4.27 (q, *J* = 6.5 Hz, 1H), 4.14 (ddd, *J* = 12.5, 4.7, 2.9 Hz, 1H), 4.00 (q, *J* = 6.5 Hz, 1H), 3.97 – 3.86 (m, 2H), 3.79 (s, 3H), 3.78 (s, 4H), 2.31 – 2.13 (m, 2H), 2.13 – 1.96 (m, 4H), 1.92 (d, *J* = 14.3 Hz, 1H), 1.81 (d, *J* = 13.0 Hz, 1H), 1.26 (d, *J* = 6.6 Hz, 3H), 1.20 (d, *J* = 6.6 Hz, 3H), 0.90 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 159.2, 154.9, 150.8, 133.1, 130.7, 129.8, 129.1, 128.5, 117.6, 114.7, 113.8, 99.7, 98.6, 96.3, 75.1, 74.6, 72.8, 70.7, 70.1, 68.3, 67.6, 65.6, 56.9, 55.8, 55.4, 30.8, 30.0, 24.5, 23.2, 17.8, 17.7, 17.3. HRMS: $(M + Na)^+$ calculated for $C_{40}H_{49}N_3O_{11}Na$ 770.3265; found 770.3269.

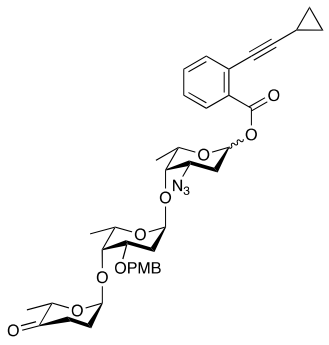
***p*-Methoxyphenyl-2,3-dideoxy-4-ulo-α-L-fucopyranosyl-(1→4)-2-deoxy-3-O-*p*-methoxybenzyl-α-L-fucopyranosyl-(1→4)-3-azido-2,3-dideoxy-α-L-fucopyranoside (42)**



A solution of **41** (819 mg, 1.10 mmol) in dioxane (80 mL), MeOH (80 mL) and 1M NaOH solution (22 mL) was heated at 60°C for 1 hour. The mixture was then concentrated *in vacuo* and partitioned between EtOAc and sat. aq. NH_4Cl. The organic layer was further washed with sat. aq. NH_4Cl and brine, dried over $MgSO_4$ and concentrated *in vacuo* to give the crude 4″-OH trisaccharide.

The above intermediate was then dissolved in DCM (100 mL), to which $NaHCO_3$ (3.20 g, 38.3 mmol, 35 eq) and Dess-Martin periodinane (1.11 g, 2.63 mmol, 2.4 eq) were added. After stirring for 2 hours, 10% aq. $Na_2S_2O_3$ (90 mL) was added and the mixture was stirred for a further 30 minutes. Then, it was washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo* to give the title compound as a light yellow thick oil (687 mg, 1.07 mmol, 98% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.31 – 7.19 (m, 2H), 7.03 – 6.93 (m, 2H), 6.93 – 6.76 (m, 4H), 5.55 (d, *J* = 2.4 Hz, 1H), 5.15 – 5.03 (m, 2H), 4.68 (q, *J* = 6.7 Hz, 1H), 4.65 – 4.46 (m, 2H), 4.30 (q, *J* = 6.5 Hz, 1H), 4.15 (ddd, *J* = 12.6, 4.8, 2.8 Hz, 1H), 4.04 – 3.94 (m, 2H), 3.91 (ddd, *J* = 9.5, 6.9, 2.7 Hz, 1H), 3.80 (s, 3H), 3.78 – 3.72 (m, 4H), 2.62 (ddd, *J* = 15.2, 9.1, 5.9 Hz, 1H), 2.41 (ddd, *J* = 15.7, 7.5, 5.6 Hz, 1H), 2.35 – 2.15 (m, 2H), 2.14 – 1.96 (m, 4H), 1.28 (d, *J* = 6.5 Hz, 3H), 1.19 (d, *J* = 6.6 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.3, 159.2, 154.9, 150.8, 130.5, 129.1, 117.6, 114.7, 113.9, 99.7, 98.0, 96.3, 75.4, 74.7, 72.7, 71.9, 70.2, 68.1, 67.6, 56.9, 55.8, 55.4, 34.1, 30.7, 30.0, 29.7, 17.7, 14.9. HRMS: $(M + Na)^+$: calculated for $C_{33}H_{43}N_3O_{10}Na$ 664.2846; found 664.2858.

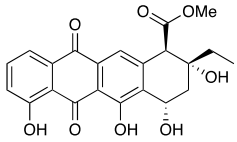
_o_-Cyclopropylethynylbenzoyl-2,3-dideoxy-4-ulo-α-L-fucopyranosyl-(1→4)-2-deoxy-3-O-_p_-methoxybenzyl-α-L-fucopyranosyl-(1→4)-3-azido-2,3-dideoxy-L-fucopyranoside (26)



To a solution of **42** (669 mg, 1.04 mmol) in 1:1 CH_3CN:H_2O (25 mL, v/v) were added NaOAc (853 mg, 10.4 mmol, 10 eq) and then $Ag(DPAH)_2 \cdot H_2O$[46] (1.00 g, 2.18 mmol, 2.1 eq) portionwise over 30 minutes at 0°C. The mixture was stirred for 130 minutes; after which it was poured into sat. aq. $NaHCO_3$. This was then extracted with DCM thrice, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (30:70 EtOAc:pentane) gave the trisaccharide lactol (479 mg, max. 0.891 mmol, 86%).

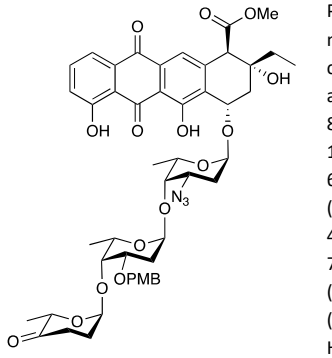
It was then subjected to General Procedure B, with final column chromatography of the residue (30:70 – 40:60 EtOAc:pentane) giving the title compound as a white solid (418 mg, 0.594 mmol, 91%, α:β 1:1.15). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.07 – 7.83 (m, 2H), 7.56 – 7.38 (m, 4H), 7.38 – 7.30 (m, 2H), 7.30 – 7.20 (m, 4H), 6.93 – 6.80 (m, 4H), 6.56 – 6.46 (m, 1H), 6.04 – 5.94 (m, 1H), 5.11 (q, *J* = 3.8 Hz, 4H), 4.69 (dq, *J* = 8.7, 6.7 Hz, 2H), 4.63 (s, 1H), 4.60 (s, 1H), 4.53 (dd, *J* = 11.5, 6.6 Hz, 2H), 4.23 (ddt, *J* = 30.3, 13.3, 6.5 Hz, 4H), 3.97 (d, *J* = 3.3 Hz, 2H), 3.92 (dtd, *J* = 13.6, 6.8, 2.7 Hz, 2H), 3.82 (s, 2H), 3.80 (dd, *J* = 4.1, 1.7 Hz, 2H), 3.76 (s, 3H), 3.74 – 3.66 (m, 3H), 2.62 (ddd, *J* = 15.2, 9.0, 5.8 Hz, 2H), 2.47 – 2.34 (m, 2H), 2.34 – 2.04 (m, 11H), 2.00 (dd, *J* = 13.1, 4.6 Hz, 1H), 1.55 – 1.40 (m, 2H), 1.34 (d, *J* = 6.5 Hz, 3H), 1.31 – 1.23 (m, 15H), 1.03 – 0.93 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.3, 165.1, 164.4, 159.2, 135.0, 134.4, 132.3, 132.1, 131.4, 131.0, 130.6, 130.4, 129.2, 129.1, 127.5, 127.1, 124.4, 113.9, 99.9, 99.8, 98.9, 98.0, 98.0, 93.0, 92.8, 75.3, 74.8, 73.6, 73.0, 72.7, 72.4, 71.9, 70.2, 70.2, 69.8, 68.2, 68.1, 59.5, 56.9, 55.4, 55.4, 34.1, 30.6, 30.2, 29.7, 28.9, 17.7, 17.7, 14.9, 9.1, 9.0, 0.8. HRMS: $(M + Na)^+$ calculated for $C_{38}H_{45}N_3O_{10}Na$ 726.3003; found 726.3006.

Aklavinone (27)[28]



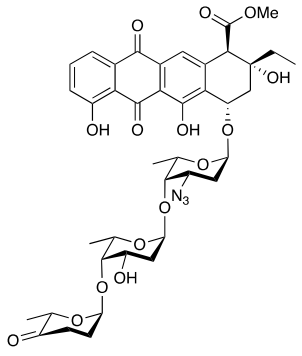
A solution of commercially available aclarubicin hydrochloride **12** (1.60 g, 1.89 mmol) in aq. HCl (0.2 M, 160 mL) was heated at 90°C for 1.5 hours. The resulting suspension was cooled down and extracted with DCM thrice. The combined organic layers were washed with sat. aq. $NaHCO_3$, dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography (2.5:97.5 MeOH:DCM) gave the title compound as a yellow solid (778 mg, 1.89 mmol, quant.). Spectral data was in accordance with that of literary precedence.[28]

7-[2,3-Dideoxy-4-ulo-α-L-fucopyranosyl-2-deoxy-3-O-_p_-methoxybenzyl-α-L-fucopyranosyl-(1→4)-3-azido-2,3-dideoxy-α-L-fucopyranoside]-aklavinone (44)



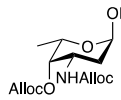
Prepared according to General Procedure C from donor **26** (52 mg, 0.071 mmol) and aklavinone **43** (2 eq) at -20°C to give after column chromatography (10:90 EtOAc:pentane and then 2:98 - 5:95 acetone:toluene) the title compound as a yellow solid (56 mg, 0.060 mmol, 85%, α:β 8:1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.70 (s, 1H), 11.96 (s, 1H), 7.80 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.73 – 7.60 (m, 2H), 7.38 – 7.09 (m, 3H), 6.93 – 6.82 (m, 2H), 5.52 (d, *J* = 3.7 Hz, 1H), 5.30 – 5.18 (m, 1H), 5.17 – 5.00 (m, 2H), 4.68 (q, *J* = 6.6 Hz, 1H), 4.65 – 4.47 (m, 2H), 4.25 (q, *J* = 6.5 Hz, 1H), 4.18 (s, 1H), 4.15 – 4.00 (m, 2H), 3.96 (d, *J* = 2.7 Hz, 1H), 3.90 (ddd, *J* = 9.7, 7.0, 2.7 Hz, 1H), 3.82 (s, 3H), 3.78 – 3.65 (m, 5H), 2.69 – 2.50 (m, 2H), 2.40 (ddd, *J* = 15.6, 7.3, 5.4 Hz, 1H), 2.33 – 2.14 (m, 3H), 2.14 – 2.05 (m, 2H), 2.00 (td, *J* = 13.2, 4.0 Hz, 1H), 1.86 (dd, *J* = 12.9, 4.4 Hz, 1H), 1.75 (dq, *J* = 14.8, 7.4 Hz, 1H), 1.51 (dq, *J* = 14.4, 7.1 Hz, 1H), 1.37 – 1.16 (m, 6H), 1.09 (t, *J* = 7.3 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.2, 192.7, 181.2, 171.3, 162.6, 162.1, 159.2, 142.6, 137.5, 133.5, 133.0, 130.9, 130.4, 129.1, 125.4, 124.9, 121.0, 120.3, 115.8, 114.8, 113.8, 101.2, 99.6, 97.9, 75.3, 74.4, 72.6, 71.8, 71.7, 71.4, 70.1, 68.0, 67.9, 57.0, 56.8, 55.4, 52.7, 34.0, 32.2, 30.6, 29.8, 29.6, 17.5, 14.8, 6.8. HRMS: $(M + Na)^+$ calculated for $C_{48}H_{55}N_3O_{16}Na$ 952.3480; found 952.3488.

7-[2,3-Dideoxy-4-ulo-α-L-fucopyranosyl-2-deoxy-3-O-α-L-fucopyranosyl-(1→4)-3-azido-2,3-dideoxy-α-L-fucopyranoside]-aklavinone (45)



To a biphasic mixture of **44** (213 mg, 0.204 mg) in DCM (34 mL) and phosphate buffer (2 mL, pH 7) was added DDQ (93 mg, 0.41 mmol, 2 eq) at 0°C after which the mixture was stirred at that temperature for 4 hours. Then, the same amount of DDQ was added and the mixture was stirred for another hour. It was then diluted with DCM, washed with H_2O four times, after which the organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography (3.5:96.5 – 20:80 acetone:toluene) gave the title compound as a yellow solid (189 mg, 0.204 mmol, 100%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.72 (s, 1H), 12.01 (s, 1H), 7.83 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.77 – 7.64 (m, 2H), 7.38 – 7.29 (m, 1H), 5.52 (d, *J* = 3.7 Hz, 1H), 5.28 – 5.26 (m, 1H), 5.15 – 5.06 (m, 1H), 5.03 (d, *J* = 3.7 Hz, 1H), 4.49 (q, *J* = 6.7 Hz, 1H), 4.37 (q, *J* = 6.3 Hz, 1H), 4.18 (s, 1H), 4.15 – 4.03 (m, 3H), 3.79 – 3.62 (m, 7H), 2.59 – 2.39 (m, 4H), 2.34 – 2.23 (m, 1H), 2.23 – 1.98 (m, 3H), 1.86 (ddd, *J* = 12.7, 9.3, 3.7 Hz, 2H), 1.75 (dq, *J* = 14.8, 7.4 Hz, 1H), 1.51 (dq, *J* = 14.3, 7.1 Hz, 1H), 1.38 – 1.19 (m, 9H), 1.08 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.2, 192.8, 181.4, 171.4, 162.7, 162.2, 142.7, 137.6, 133.6, 133.2, 125.0, 121.1, 120.4, 115.9, 114.9, 101.2, 100.3, 99.9, 82.8, 75.1, 71.9, 71.8, 71.4, 67.9, 67.4, 65.4, 57.1, 56.9, 52.7, 34.1, 33.6, 32.2, 29.9, 29.8, 27.7, 17.5, 17.2, 14.9, 6.8. HRMS: $(M + Na)^+$ calculated for $C_{40}H_{47}N_3O_{15}Na$ 832.2905; found 832.2916.

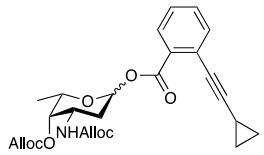
***p*-Methoxyphenyl-4-*O*-allyloxycarbonyl-3-*N*-allyloxycarbonyl-2,3-dideoxy-α-L-fucopyranoside (49)**



To a solution of **28** (838 mg, 3.00 mmol) in THF:H_2O (16.5 mL, 10:1 v/v) was added triphenylphosphine (1.57 g, 6.00 mmol, 2 eq) and the mixture was stirred overnight. It was then filtered off and concentrated *in vacuo*.

The above crude amine was then dissolved in DCM (21.5 mL) and brought to 0°C. At this temperature, pyridine (1.45 mL, 18.0 mmol, 6 eq) and allyloxycarbonyl chloroformate (0.96 mL, 9.00 mmol, 3 eq) were added consecutively. After being allowed up to room temperature for 3 hours, another portion of both reagents was added again, and another after 2 more hours. Then after stirring overnight, H_2O (10 mL) was added and the mixture was stirred vigorously for 10 minutes. It was then washed with sat aq. $NaHCO_3$ and H_2O twice. Drying over $MgSO_4$ and concentration *in vacuo* gave a residue that was subjected to column chromatography (10:90 – 17:83 EtOAc:pentane) gave the di-Alloc glycoside as a yellow solid (528 mg, 1.26 mmol, 42% over 2 steps, 1:20 α:β). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.09 – 6.90 (m, 2H), 6.90 – 6.71 (m, 2H), 6.10 – 5.79 (m, 2H), 5.55 (d, *J* = 3.2 Hz, 1H), 5.46 – 5.18 (m, 4H), 4.99 (d, *J* = 2.9 Hz, 1H), 4.83 (d, *J* = 8.8 Hz, 1H), 4.73 – 4.61 (m, 2H), 4.59 (d, *J* = 5.7 Hz, 2H), 4.56 – 4.47 (m, 1H), 4.19 (q, *J* = 6.7 Hz, 1H), 3.77 (s, 3H), 2.05 (ddt, *J* = 13.0, 5.3, 1.3 Hz, 1H), 1.97 (td, *J* = 12.7, 3.4 Hz, 1H), 1.14 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4, 155.3, 154.8, 150.8, 132.8, 131.4, 119.4, 118.1, 117.5, 114.7, 96.0, 75.4, 69.0, 66.0, 65.8, 55.8, 45.6, 31.1, 16.8. HRMS: $(M + Na)^+$ calculated for $C_{21}H_{27}NO_8Na$ 444.1634; found 444.1634.

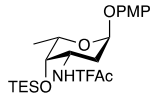
***o*-Cyclopropylethynylbenzoyl-3-*N*-allyloxycarbonyl-4-*O*-allyloxycarbonyl-2,3-dideoxy-L-fucopyranoside (52)**



Prepared according to General Procedure A and B from the above glycoside (210 mg, 0.50 mmol), to give after column chromatography (4:96 Et_2O:pentane – 10:90 – 20:80 EtOAc:pentane) the title compound as a light yellow wax (237 mg, 0.49 mmol, 98% over 2 steps). Spectral data for the α-anomer: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.93 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.49 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.43 (td, *J* = 7.6, 1.4 Hz, 1H), 7.32 (td, *J* = 7.6, 1.4 Hz, 1H), 6.52 (t, *J* = 2.5 Hz, 1H), 6.08 – 5.79 (m, 2H), 5.49 – 5.16 (m, 4H), 5.07 (d, *J* = 2.9 Hz, 1H), 4.80 (d, *J* = 8.5 Hz, 1H), 4.73 – 4.60 (m, 2H), 4.56 (d, *J* = 5.6 Hz, 2H), 4.50 (t, *J* = 8.4 Hz, 1H), 4.43 (q, *J* = 6.5 Hz, 1H), 2.10 – 1.99 (m, 2H), 1.61 (dd, *J* = 8.2, 5.2 Hz, 1H), 1.23 (d, *J* = 6.6 Hz, 3H), 0.97 – 0.72 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.9, 155.3, 134.9, 132.7, 132.1, 131.4, 131.3, 130.9, 127.4, 124.9, 119.5, 118.0, 92.6, 74.9, 69.1, 68.1, 66.0, 45.8, 29.9, 16.9, 9.0, 0.7. Spectral data for the β-anomer: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.94 (ddd, *J* = 8.0, 1.4, 0.5 Hz, 1H), 7.48 (ddd, *J* = 7.8, 1.5, 0.5 Hz, 1H), 7.42 (td, *J* = 7.6, 1.4 Hz, 1H), 7.29 (ddd, *J* = 8.0, 7.3, 1.4 Hz, 1H), 6.10 – 5.82 (m, 3H), 5.44 – 5.16 (m, 4H), 4.93 (d, *J* = 3.0 Hz, 1H), 4.90 (d, *J* = 8.8 Hz, 1H), 4.68 (tdt, *J* = 14.1, 5.8, 1.4 Hz, 2H), 4.58 (d, *J* = 5.7 Hz, 2H), 4.21 – 4.09 (m, 1H),

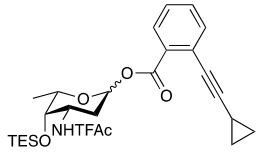
3.90 (q, *J* = 6.5 Hz, 1H), 2.12 (dddd, *J* = 12.2, 4.8, 2.5, 0.9 Hz, 1H), 1.94 (ddd, *J* = 13.0, 12.1, 9.9 Hz, 1H), 1.56 – 1.48 (m, 1H), 1.28 (d, *J* = 6.5 Hz, 3H), 0.92 – 0.87 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.2, 155.2, 134.3, 132.7, 132.2, 131.4, 130.9, 130.7, 127.1, 125.3, 119.4, 118.2, 100.0, 92.8, 74.5, 74.0, 71.6, 69.1, 66.1, 49.0, 31.6, 16.8, 9.0, 0.8. HRMS: (M + Na)$^+$ calculated for $C_{26}H_{29}NO_8Na$ 506.1791; found 506.1796.

_p_-Methoxyphenyl-3-trifluoroacetylamino-2,3-dideoxy-4-triethylsilyl-α-L-fucopyranoside (50)



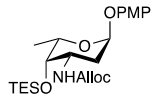
A solution of **48** (Chapter 2) (1.23 g, 4.40 mmol) and triphenylphosphine (4.6 g, 17.6 mmol, 4 eq) in THF:H_2O (10:1 v/v, 165 mL) was stirred overnight. It was then concentrated *in vacuo* and coevaporated twice with toluene before being used immediately in the next step. To a solution above free amine in DCM (150 mL) were added Et_3N (1.7 mL, 12.3 mmol, 2.8 eq) and trifluoroacetic anhydride (871 µL, 6.16 mmol, 1.4 eq) at 0 °C. The resulting mixture was stirred for 2 hours, after which it was quenched by addition of H_2O (10 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (10:90 – 20:80 Et_2O:pentane) gave the title compound as a clear oil (2.03 g, 4.40 mmol, quant. over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, *J* = 8.0 Hz, 2H), 6.82 (d, *J* = 8.0 Hz, 2H), 6.38 (d, *J* = 8.0 Hz, 1H), 5.53 (s, 1H), 4.66 (s, 1H), 4.05 (d, *J* = 6.1 Hz, 1H), 3.80 (s, 1H), 3.77 (s, 3H), 2.12 (t, *J* = 12.5 Hz, 1H), 1.93 (d, *J* = 12.1 Hz, 1H), 1.15 (d, *J* = 6.0 Hz, 3H), 1.00 (t, *J* = 7.7 Hz, 9H), 0.78 – 0.58 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.1, 156.7, 156.3, 156.0, 154.8, 150.9, 117.6, 114.7, 95.8, 70.8, 67.2, 55.7, 46.8, 30.0, 17.6, 7.1, 5.4. HRMS: [M + H]$^+$ calculated for $C_{21}H_{33}F_3NO_5Si$ 464.20746; found 464.20724.

***o*-Cyclopropylethynylbenzoyl-2,3-dideoxy-4-*O*-triethylsilyl-3-*N*-trifluoroacetyl-L-fucopyranoside (36)**



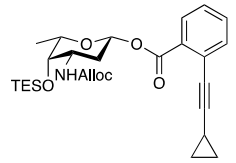
Prepared according to General Procedure A and B from (Chapter 2) (95 mg, 0.21 mmol), to give after column chromatography (4:96 - 20:80 EtOAc:pentane) the title compound as a light yellow wax (66 mg, 0.12 mmol, 68% over 2 steps, 1:4 α:β). Spectral data for the β-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.95 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.48 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.42 (td, *J* = 7.5, 1.3 Hz, 1H), 7.29 (dd, *J* = 7.7, 1.5 Hz, 1H), 6.44 (d, *J* = 8.9 Hz, 1H), 6.09 – 5.85 (m, 1H), 4.36 – 4.17 (m, 1H), 3.83 – 3.69 (m, 2H), 2.14 – 2.00 (m, 2H), 1.51 (pd, *J* = 6.2, 2.6 Hz, 1H), 1.30 (d, *J* = 6.4 Hz, 3H), 1.01 (td, *J* = 8.0, 2.7 Hz, 9H), 0.90 – 0.87 (m, 4H), 0.78 – 0.59 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 157.0, 156.6, 156.2, 155.9, 148.5, 134.3, 132.1, 130.8, 130.7, 127.0, 125.2, 122.7, 99.9, 92.9, 74.5, 69.7, 49.7, 30.6, 17.6, 9.0, 7.0, 5.4, 0.8. HRMS: [M + H]$^+$ calculated for $C_{21}H_{33}F_3NO_5Si$ 548.20560; found 548.20496.

***p*-Methoxyphenyl-3-N-allyloxycarbonyl-2,3-dideoxy-4-triethylsilyl-α-L-fucopyranoside (51)**



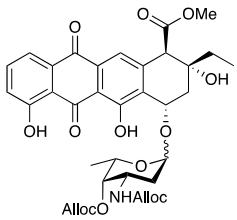
To a solution of **48** (Chapter 2) (862 mg, 2.19 mmol) in THF/H_2O (80 mL, 10:1 v/v) was added polymer-bound PPh_3 (1.46 g, 4.38 mmol, 2 eq) and the mixture was stirred overnight at 50 °C. Then, an additional portion of polymer-bound PPh_3 (0.73 g, 2.19 mmol, 1 eq) and the mixture was stirred an additional night at 50 °C. It was then filtered off and concentrated *in vacuo*. The resulting amine was dissolved in DCM (15.7 mL) to which pyridine (0.53 mL, 6.57 mmol, 3 eq) and allyl chloroformate (0.35 mL, 3.29 mmol, 1.5 eq) were added at -20 °C. After stirring at that temperature for 15 minutes, the reaction was allowed to warm up to RT, and poured into sat. aq. $NaHCO_3$. The organic layer was separated, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (5:95 – 10:90 EtOAc:pentane) gave the title compound as a yellow oil (870 mg, 1.93 mmol, 88% over 2 steps). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.05 – 6.90 (m, 2H), 6.86 – 6.73 (m, 2H), 5.94 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.51 (d, *J* = 2.9 Hz, 1H), 5.33 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.23 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.76 (d, *J* = 9.1 Hz, 1H), 4.60 (qdt, *J* = 13.4, 5.8, 1.5 Hz, 2H), 4.35 – 4.27 (m, 1H), 4.01 (q, *J* = 6.5 Hz, 1H), 3.79 (d, *J* = 2.6 Hz, 1H), 3.77 (s, 3H), 2.01 (td, *J* = 12.7, 3.5 Hz, 1H), 1.86 (dd, *J* = 12.5, 4.4 Hz, 1H), 1.13 (d, *J* = 6.5 Hz, 3H), 1.00 (t, *J* = 7.9 Hz, 9H), 0.67 (qd, *J* = 7.9, 3.2 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.5, 154.6, 151.1, 133.0, 117.8, 117.5, 114.7, 96.2, 71.4, 67.4, 65.7, 55.8, 47.5, 30.6, 17.7, 7.2, 5.4. HRMS: [M + Na]$^+$ calculated for $C_{23}H_{37}NO_6SiNa$: 474.2288; found 474.2288.

_o_-Cyclopropylethynylbenzoyl-3-_N_-allyloxycarbonyl-2,3-dideoxy-4-triethylsilyl-β-L-fucopyranoside (54)



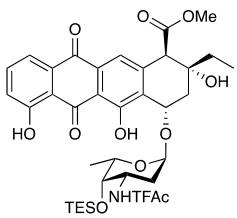
Prepared according to General Procedure A and B from **51** (225 mg, 0.500 mmol), to give after column chromatography (5:95 – 30:70 EtOAc:pentane) gave the title compound as a clear oil (158 mg, 0.308 mmol, 61% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.96 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.47 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.41 (td, *J* = 7.5, 1.4 Hz, 1H), 7.30 (dd, *J* = 7.2, 5.7 Hz, 1H), 6.01 – 5.84 (m, 2H), 5.40 – 5.17 (m, 2H), 4.84 (d, *J* = 9.1 Hz, 1H), 4.59 (qdt, *J* = 13.3, 5.8, 1.5 Hz, 2H), 3.93 (qd, *J* = 9.0, 2.7 Hz, 1H), 3.78 – 3.62 (m, 2H), 2.00 – 1.87 (m, 2H), 1.51 (tt, *J* = 7.2, 5.8 Hz, 1H), 1.28 (d, *J* = 6.4 Hz, 3H), 1.00 (t, *J* = 7.9 Hz, 9H), 0.94 – 0.82 (m, 4H), 0.67 (qd, *J* = 7.8, 2.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 155.4, 134.3, 132.8, 132.0, 130.9, 127.0, 125.2, 117.9, 99.8, 93.4, 74.6, 73.1, 70.3, 65.8, 50.8, 31.1, 17.6, 9.0, 7.2, 5.4, 0.8. HRMS: [M + Na]$^+$ calculated for $C_{28}H_{39}NO_6SiNa$ 536.2444; found 536.2449.

7-[3-_N_-allyloxycarbonyl-4-_O_-allyloxycarbonyl-2,3-dideoxy-L-fucopyranoside]-aklavinone (55)



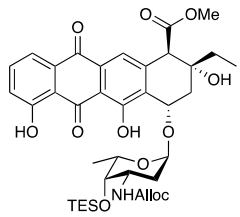
Prepared according to General Procedure C from donor **52** and aklavinone **43** (2 eq) at variable temperature to give after column chromatography (2:98 acetone:toluene) the title compound as a yellow solid. -78 °C to 0 °C (85%, 6.3:1 α:β), -20 °C (93%, 6.7:1 α:β) or RT (58%, 6.6:1 α:β). Spectral data for the α-anomer: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 12.67 (d, *J* = 4.2 Hz, 1H), 11.99 (s, 1H), 7.86 – 7.78 (m, 1H), 7.75 – 7.59 (m, 2H), 7.27 (dd, *J* = 4.5, 1.2 Hz, 1H), 6.06 – 5.76 (m, 2H), 5.49 (d, *J* = 3.5 Hz, 1H), 5.44 – 5.12 (m, 5H), 5.01 – 4.95 (m, 1H), 4.75 (d, *J* = 8.4 Hz, 1H), 4.72 – 4.60 (m, 2H), 4.60 – 4.53 (m, 1H), 4.48 (d, *J* = 5.7 Hz, 1H), 4.30 (q, *J* = 6.6 Hz, 1H), 4.12 (d, *J* = 1.3 Hz, 1H), 4.10 – 4.01 (m, 1H), 3.69 (s, 3H), 2.59 – 2.50 (m, 1H), 2.35 – 2.27 (m, 1H), 1.97 – 1.83 (m, 2H), 1.82 – 1.67 (m, 1H), 1.50 (dq, *J* = 13.8, 7.0 Hz, 1H), 1.25 (d, *J* = 6.5 Hz, 3H), 1.09 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.8, 181.4, 171.5, 162.6, 162.2, 155.2, 142.8, 137.5, 133.6, 133.1, 131.4, 131.0, 129.1, 128.3, 124.9, 121.1, 120.3, 119.4, 117.9, 115.9, 114.8, 101.3, 75.1, 71.8, 71.5, 69.0, 66.1, 65.8, 57.1, 52.6, 45.6, 34.1, 32.2, 31.0, 16.8, 6.8. ^{13}C-GATED NMR ($CDCl_3$, 126 MHz) δ 101.3 ($J_{C1,\ H1}$ = 171.15 Hz). Spectral data for the β -anomer: ^{13}C-GATED NMR ($CDCl_3$, 126 MHz) δ 99.2 ($J_{C1,\ H1}$ = 158.60 Hz). HRMS: [M + Na]$^+$ calculated for $C_{36}H_{39}NO_{14}Na$ 732.2268; found 732.2285.

7-[2,3-Dideoxy-4-_O_-triethylsilyl-3-_N_-trifluoroacetyl-α-L-fucopyranoside]-aklavinone (56)



Prepared according to General Procedure C from donor **53** and aklavinone **43** (2 eq) at RT to give after column chromatography (10:90 – 20:80 EtOAc:pentane) the title compound as a yellow solid (54 mg, 0.072 mmol, 59%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 12.67 (s, 1H), 11.98 (s, 1H), 7.80 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.77 – 7.63 (m, 2H), 7.34 – 7.23 (m, 2H), 6.23 (d, *J* = 8.7 Hz, 1H), 5.48 (d, *J* = 3.8 Hz, 1H), 5.32 – 5.11 (m, 1H), 4.24 – 4.17 (m, 1H), 4.14 (d, *J* = 6.6 Hz, 1H), 4.13 – 4.09 (m, 2H), 3.79 (d, *J* = 2.6 Hz, 1H), 3.70 (s, 3H), 2.54 (dd, *J* = 15.1, 4.4 Hz, 1H), 2.33 (dt, *J* = 15.0, 1.8 Hz, 1H), 2.03 (td, *J* = 12.8, 4.2 Hz, 1H), 1.82 (dt, *J* = 13.3, 6.6 Hz, 1H), 1.75 (dq, *J* = 14.7, 7.3 Hz, 1H), 1.51 (dq, *J* = 14.5, 7.3 Hz, 1H), 1.31 – 1.20 (m, 83H), 1.09 (t, *J* = 7.4 Hz, 3H), 1.00 (t, *J* = 8.0 Hz, 9H), 0.76 – 0.57 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.8, 181.4, 171.5, 162.7, 162.2, 156.7, 156.4, 156.1, 155.8, 142.7, 137.5, 133.6, 133.1, 131.0, 124.9, 121.1, 120.3, 115.9, 114.8, 101.1, 71.7, 71.6, 70.5, 67.4, 57.1, 52.6, 46.8, 34.1, 32.2, 30.0, 17.6, 7.0, 6.8, 5.4. HRMS: [M + Na]$^+$ calculated for $C_{36}H_{44}F_3NO_{11}SiNa$ 762.2922; found 762.2938.

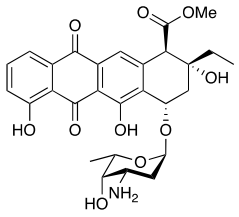
7-[3-_N_-allyloxycarbonyl-2,3-dideoxy-α-L-fucopyranoside]-aklavinone (57)



Prepared according to General Procedure C from donor **54** and aklavinone **43** (2 eq) at RT to give after column chromatography (4:96 Et_2O:pentane and then 1.5:98.5 acetone:toluene) the title compound as a yellow solid (149 mg, 0.201 mmol, 73%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.66 (s, 1H), 12.04 (s, 1H), 7.83 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.77 – 7.64 (m, 2H), 7.31 (dd, *J* = 8.4, 1.2 Hz, 1H), 5.86 (ddt, *J* = 16.3, 10.8, 5.6 Hz, 1H), 5.46 (d, *J* = 3.8 Hz, 1H), 5.28 – 5.12 (m, 3H), 4.63 (d, *J* = 8.8 Hz, 1H), 4.58 – 4.41 (m, 2H), 4.21 (s, 1H), 4.15 – 4.01 (m, 2H), 3.86 (dq, *J* = 8.7, 4.1 Hz, 1H), 3.78 (s, 1H), 3.69 (s, 3H), 2.50 (dd, *J* = 15.0, 4.4 Hz, 1H), 2.34 (d, *J* = 15.0 Hz, 1H), 1.92 (td,

J = 12.8, 4.1 Hz, 1H), 1.81 – 1.68 (m, 2H), 1.49 (dq, *J* = 14.3, 7.3 Hz, 1H), 1.36 – 1.18 (m, 3H), 1.08 (t, *J* = 7.3 Hz, 3H), 0.99 (t, *J* = 7.9 Hz, 9H), 0.66 (qd, *J* = 7.9, 2.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.9, 181.5, 171.6, 162.7, 162.3, 155.2, 142.9, 137.5, 133.7, 133.0, 132.9, 131.3, 124.9, 121.1, 120.3, 117.8, 115.9, 114.8, 101.6, 71.5, 71.4, 71.1, 67.6, 65.6, 57.2, 52.6, 47.4, 34.0, 32.2, 30.4, 17.6, 7.2, 6.8, 5.4. HRMS: $[M + Na]^+$ calculated for $C_{38}H_{49}NO_{12}SiNa$ 774.2533; found 774.2525.

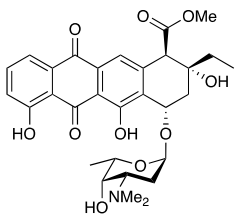
7-[α-L-Daunosamino]-aklavinone (2)



To a solution of **57** (60 mg, 0.081 mmol) in DCM (8.1 mL) were added *N,N*-dimethylbarbituric acid (38 mg, 0.24 mmol, 3 eq) and tetrakis(triphenylphosphine) palladium(0) (4.6 mg, 4.1 µmol, 0.05 eq). After stirring for 2.5 hours, the mixture was concentrated *in vacuo*. Column chromatography (DCM – 2:98 MeOH:DCM) gave the crude amine.

This was then redissolved in pyridine (6 mL) in a PTFE tube, after which HF.pyr complex (70 wt% HF, 710 µL) was added at 0°C. After 3.5 hours and 5.5 hours, additional HF.pyr complex (70 wt% HF, 355 µL each time) was added. After stirring for a total of 6.5 hours, solid $NaHCO_3$ was added to quench and the mixture was stirred until cessation of effervescence. It was then filtered off, and the filter cake was rinsed thoroughly with MeOH:DCM (9:1 v/v). The combined filtrates were then concentrated *in vacuo*. Column chromatography (DCM – 20:80 MeOH:DCM) gave the title compound as a yellow solid (18 mg, 33 µmol, 41% over 2 steps). ^{1}H NMR (500 MHz, Methanol-*d*$_4$) δ 7.77 – 7.61 (m, 2H), 7.53 (s, 1H), 7.31 – 7.20 (m, 1H), 5.49 (s, 1H), 5.14 (d, *J* = 4.7 Hz, 1H), 4.27 (q, *J* = 6.5 Hz, 1H), 4.08 (s, 1H), 3.73 (s, 2H), 3.67 (d, *J* = 2.8 Hz, 1H), 3.57 – 3.47 (m, 1H), 2.52 (dd, *J* = 15.0, 5.2 Hz, 1H), 2.32 (d, *J* = 15.0 Hz, 1H), 2.03 (td, *J* = 12.9, 4.0 Hz, 1H), 1.99 – 1.90 (m, 1H), 1.76 (dq, *J* = 14.7, 7.4 Hz, 1H), 1.56 (dq, *J* = 13.9, 7.1 Hz, 1H), 1.31 (d, *J* = 6.6 Hz, 3H), 1.11 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, MeOD) δ 193.6, 182.3, 172.6, 163.7, 143.8, 138.5, 134.7, 134.0, 125.8, 121.2, 120.8, 117.0, 115.8, 101.7, 72.5, 72.1, 68.4, 68.1, 58.2, 53.0, 49.8, 48.4, 35.8, 33.3, 30.1, 17.0, 7.1. HRMS: $[M + H]^+$ calculated for $C_{28}H_{32}NO_{10}$ 542.2026; found 542.2031.

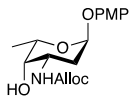
7-[α-L-Rhodosamino]-aklavinone (aklavin) (4)



To a solution of **57** (23.7 mg, 0.032 mmol) in DCM (3.2 mL) were added *N,N*-dimethylbarbituric acid (15 mg, 0.096 mmol, 3 eq) and tetrakis(triphenylphosphine)palladium(0) (1.8 mg, 1.6 µmol, 0.05 eq). After stirring for 2.5 hours, the mixture was concentrated *in vacuo*. Column chromatography (DCM – 2:98 MeOH:DCM) gave the crude amine.

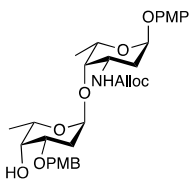
This was then redissolved in EtOH (7.7 mL) and 37% aq. CH_2O (79 µL, 30 eq) was added $NaBH(OAc)_3$ (67 mg, 0.32 mmol, 10 eq). The mixture was stirred for 2.5 hours before being quenched by addition of sat. aq. $NaHCO_3$. It was then poured into H_2O and extracted with DCM, dried over Na_2SO_4 and concentrated *in vacuo* to give the crude dimethylated amine. This was then redissolved in pyridine (3.2 mL) in a PTFE tube, after which HF.pyr complex (70 wt% HF, 125 µL) was added at 0 °C. Over the course of 4 hours, additional HF.pyr complex (70 wt% HF, 125 µL each time) was added 5 times. Solid $NaHCO_3$ was added to quench and the mixture was stirred until cessation of effervescence. It was then filtered off, and the filtrate was partitioned between DCM/H_2O. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography on neutral silica (DCM – 20:80 MeOH:DCM) gave the title compound as a yellow solid (7.9 mg, 13.9 µmol, 43% over 3 steps). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 12.70 (s, 1H), 12.01 (s, 1H), 7.83 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.77 – 7.66 (m, 2H), 7.31 (dd, *J* = 8.4, 1.2 Hz, 1H), 5.55 (d, *J* = 3.9 Hz, 1H), 5.29 – 5.20 (m, 1H), 4.27 (s, 1H), 4.16 – 4.03 (m, 2H), 3.87 (s, 1H), 3.70 (s, 3H), 2.54 (dd, *J* = 15.2, 4.5 Hz, 1H), 2.45 (s, 6H), 2.33 (d, *J* = 15.2 Hz, 1H), 2.05 (td, *J* = 13.1, 12.6, 4.2 Hz, 1H), 1.89 (dd, *J* = 12.9, 4.6 Hz, 1H), 1.76 (dq, *J* = 14.6, 7.3 Hz, 1H), 1.52 (dq, *J* = 14.5, 7.3 Hz, 1H), 1.38 (dd, *J* = 6.5, 2.1 Hz, 3H), 1.09 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.9, 181.4, 171.3, 162.8, 162.3, 142.8, 137.6, 133.6, 133.1, 131.2, 125.0, 121.1, 120.4, 115.9, 114.9, 101.1, 71.9, 71.4, 67.0, 65.8, 61.1, 57.2, 52.7, 42.0, 34.0, 32.2, 27.8, 17.0, 6.8. HRMS: $[M + H]^+$ calculated for $C_{30}H_{36}NO_{10}$ 570.2339; found 570.2921.

***p*-Methoxyphenyl-3-*N*-allyloxycarbonyl-2,3-dideoxy-α-L-fucopyranoside (58)**



To a solution of **28** (838 mg, 3.00 mmol) in THF/H_2O (10:1 v/v, 16.5 mL) was added polymer-bound triphenylphosphine (3 mmol/g, 2.00g, 3 eq) and the mixture was stirred for 4 nights. To this mixture were then added $NaHCO_3$ (504 mg, 6 mmol, 2 eq), H_2O (10 mL) and finally *N*-(allyloxycarbonyloxy)succinimide (956 mg, 4.8 mmol, 1.6 eq). After stirring for 3 hours, it was partitioned between EtOAc and H_2O, and the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (30:70:1– 40:60:1 EtOAc:pentane:Et_3N) gave the title compound as a white solid (904 mg, 2.67 mmol, 89% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.06 – 6.91 (m, 2H), 6.91 – 6.74 (m, 2H), 5.94 (ddt, *J* = 16.4, 10.9, 5.6 Hz, 1H), 5.48 (d, *J* = 3.4 Hz, 1H), 5.41 – 5.29 (m, 1H), 5.29 – 5.16 (m, 2H), 4.59 (d, *J* = 5.7 Hz, 2H), 4.39 – 4.22 (m, 1H), 4.15 (q, *J* = 6.5 Hz, 1H), 3.77 (s, 3H), 3.67 (s, 1H), 2.08 (ddt, *J* = 13.2, 5.0, 1.1 Hz, 1H), 194 (bs, 1H), 1.87 (td, *J* = 12.9, 3.7 Hz, 1H), 1.19 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7, 154.8, 150.9, 132.9, 118.0, 117.6, 114.7, 96.2, 77.5, 77.2, 76.8, 70.0, 65.8, 55.8, 47.1, 30.8, 16.9. HRMS: $[M + Na]^+$ calculated for $C_{17}H_{23}NO_6Na$ 360.1423; found 360.1416.

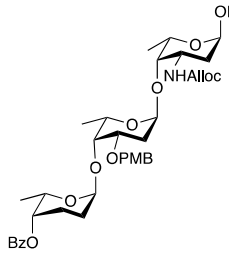
***p*-Methoxyphenyl-2-deoxy-3-O-*p*-methoxybenzyl-α-L-fucopyranosyl-(1→4)-3-*N*-allyloxycarbonyl-2,3-dideoxy-α-L-fucopyranoside (59)**



Method 1: To a solution of the glycosyl acceptor **58** (169 mg g, 0.5 mmol, 1 eq) and the glycosyl donor **29** (325 mg, 0.7 mmol, 1.4 eq) in 4:1 Et_2O:DCE (15 mL, v/v), activated molecular sieves (4Å) were added. The mixture was stirred for 30 minutes and then, at 10°C, iodonium dicollidine perchlorate (937 mg, 2.00 mmol, 4 eq) was added. After 30 minutes, triphenylphosphine (262 mg, 1.00 mmol, 2 eq) was added and the mixture was stirred for an additional hour. It was then diluted with EtOAc and filtered, washed with 10% aq. $Na_2S_2O_3$, 1M $CuSO_4$ solution twice, H_2O and then dried over $MgSO_4$. Concentration *in vacuo* and column chromatography (15:85 – 20:80 EtOAc:pentane) of the residue gave the disaccharide. This was then dissolved in in MeOH (8.8 mL) and DCM (8.8 mL), after which NaOMe was added to pH=10. After stirring for a week, it was neutralized by addition of dry ice and concentrated *in vacuo*. Column chromatography (20:80 – 50:50 EtOAc:pentane) gave the title compound as a clear oil (232 mg, 0.39 mmol, 78% over 2 steps).

Method 2: To a solution of **40** (1.14 g, 2.15 mmol) in THF/H_2O (10:1 v/v, 24 mL) was added polymer-bound triphenylphosphine (3 mmol/g, 1.43 g, 2 eq) and the mixture was stirred overnight at 50°C. To this mixture were then added $NaHCO_3$ (470 mg, 5.59 mmol, 2.6 eq), H_2O (7.2 mL) and finally *N*-(allyloxycarbonyloxy)succinimide (557 mg, 2.8 mmol, 1.3 eq). After stirring for 2 nights, it was partitioned between EtOAc and H_2O, and the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (30:70– 40:60 EtOAc:pentane) gave the title compound as a white solid (1.20 g, 2.04 mmol, 95% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.28 (d, *J* = 6.7 Hz, 2H), 7.05 – 6.96 (m, 2H), 6.96 – 6.87 (m, 2H), 6.87 – 6.77 (m, 2H), 6.21 (d, *J* = 8.2 Hz, 1H), 5.92 (ddt, *J* = 16.4, 10.9, 5.5 Hz, 1H), 5.51 (d, *J* = 3.1 Hz, 1H), 5.37 – 5.25 (m, 1H), 5.20 (dt, *J* = 10.4, 1.4 Hz, 1H), 5.00 – 4.92 (m, 1H), 4.62 – 4.52 (m, 4H), 4.39 – 4.25 (m, 1H), 4.11 (q, *J* = 7.8, 7.1 Hz, 1H), 4.08 – 4.01 (m, 1H), 3.97 (td, *J* = 8.4, 3.1 Hz, 1H), 3.86 (s, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.56 (s, 1H), 2.21 (s, 1H), 2.13 (dd, *J* = 12.6, 4.5 Hz, 1H), 2.08 – 2.00 (m, 2H), 1.86 (td, *J* = 12.7, 3.5 Hz, 1H), 1.38 (d, *J* = 6.6 Hz, 3H), 1.17 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 155.9, 154.7, 151.1, 133.0, 130.0, 129.5, 117.6, 117.5, 114.6, 114.1, 101.4, 96.4, 81.5, 72.7, 70.2, 68.2, 67.5, 67.2, 65.7, 55.8, 55.4, 46.6, 31.8, 30.3, 17.4, 16.8. HRMS: $[M + Na]^+$ calculated for $C_{31}H_{41}NO_{10}Na$ 610.2628; found 610.2632.

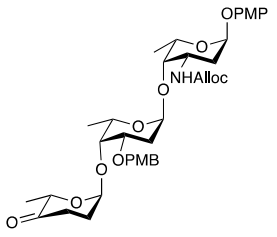
***p*-Methoxyphenyl-4-O-benzoyl-2,3-dideoxy-α-L-fucopyranosyl-(1→4)-2-deoxy-3-O-*p*-methoxybenzyl-α-L-fucopyranosyl-(1→4)-3-*N*-allyloxycarbonyl-2,3-dideoxy-α-L-fucopyranoside (60)**



To a solution of the glycosyl acceptor **59** (120 g, 2.04 mmol) and the glycosyl donor **30α** (1.01 g, 2.86 mmol, 1.4 eq) in 4:1 Et_2O:DCE (62.5 mL, v/v), activated molecular sieves (4Å) were added. The mixture was stirred for 30 minutes and then, at 10°C, iodonium dicollidine perchlorate (3.82 g, 8.16 mmol, 4 eq) was added. After 35 minutes, triphenylphosphine (1.07g, 4.08 mmol, 2.00 eq) was added and the mixture was stirred for an additional hour. It was then diluted with EtOAc and filtered, washed with 10% aq. $Na_2S_2O_3$, 1M $CuSO_4$ solution twice, H_2O and then dried over $MgSO_4$. Concentration *in vacuo* and column chromatography (10:90 – 30:70 EtOAc:pentane) of the residue gave the title

compound as a thick clear oil (1.59 g, 1.97 mmol, 97%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.12 – 8.05 (m, 2H), 7.61 – 7.54 (m, 1H), 7.51 – 7.37 (m, 2H), 7.28 (d, *J* = 2.2 Hz, 2H), 7.04 – 6.94 (m, 2H), 6.92 – 6.85 (m, 2H), 6.85 – 6.76 (m, 2H), 6.16 (d, *J* = 8.3 Hz, 1H), 5.92 (ddt, *J* = 16.3, 10.8, 5.6 Hz, 1H), 5.49 (d, *J* = 2.7 Hz, 1H), 5.34 – 5.16 (m, 2H), 5.04 (s, 1H), 5.03 – 4.94 (m, 2H), 4.72 – 4.50 (m, 5H), 4.40 – 4.25 (m, 1H), 4.17 – 4.01 (m, 2H), 3.99 – 3.88 (m, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 3.56 (s, 1H), 2.29 – 2.15 (m, 2H), 2.14 – 1.98 (m, 3H), 1.94 (d, *J* = 14.0 Hz, 1H), 1.88 – 1.76 (m, 2H), 1.31 (d, *J* = 6.5 Hz, 3H), 1.16 (d, *J* = 6.5 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 159.2, 155.9, 154.7, 151.1, 133.1, 130.6, 130.5, 129.8, 129.0, 128.5, 117.7, 117.6, 114.6, 113.9, 101.5, 98.7, 96.4, 81.1, 77.5, 77.4, 77.2, 76.8, 74.9, 72.7, 70.6, 70.3, 70.3, 68.8, 67.5, 65.7, 65.7, 65.7, 55.8, 55.4, 46.6, 31.8, 31.3, 24.5, 23.1, 17.5, 17.2. HRMS: $[M + Na]^+$ calculated for $C_{44}H_{55}NO_{13}Na$ 828.3571; found 828.3586.

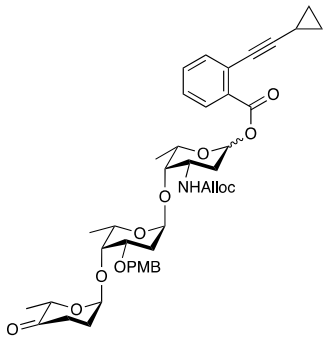
***p*-Methoxyphenyl-2,3-dideoxy-4-ulo-α-L-fucopyranosyl-(1→4)-2-deoxy-3-O-*p*-methoxybenzyl-α-L-fucopyranosyl-(1→4)-3-azido-2,3-dideoxy-α-L-fucopyranoside (61)**



Trisaccharide **60** (1.20 g, 2.04 mmol) was dissolved in in MeOH (40 mL) and DCM (40 mL), after which NaOMe was added to pH 10. After stirring for a week, it was neutralized by addition of dry ice and concentrated *in vacuo*. Column chromatography (50:50 – 75:25 EtOAc:pentane) gave the title compound as a white foam (1.21 g, 1.72 mmol, 85%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.32 – 7.19 (m, 2H), 7.05 – 6.95 (m, 2H), 6.93 – 6.85 (m, 2H), 6.85 – 6.75 (m, 2H), 6.15 (d, *J* = 8.3 Hz, 1H), 5.97 – 5.86 (m, 1H), 5.49 (d, *J* = 3.1 Hz, 1H), 5.30 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.20 (dq, *J* = 10.6, 1.5 Hz, 1H), 4.99 (q, *J* = 1.5 Hz, 1H), 4.92 (d, *J* = 3.2 Hz, 1H), 4.70 – 4.46 (m, 4H), 4.43 – 4.34 (m, 1H), 4.31 (dt, *J* = 7.8, 4.3 Hz, 1H), 4.09 (q, *J* = 6.3 Hz, 1H), 4.01 (q, *J* = 6.6 Hz, 1H), 3.96 – 3.86 (m, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 3.54 (s, 1H), 3.52 (s, 1H), 2.17 (td, *J* = 12.1, 3.7 Hz, 1H), 2.12 – 1.90 (m, 4H), 1.82 (td, *J* = 12.6, 3.5 Hz, 1H), 1.78 – 1.66 (m, 3H), 1.29 (d, *J* = 6.6 Hz, 3H), 1.14 (d, *J* = 6.5 Hz, 3H), 0.91 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 155.9, 154.6, 151.1, 133.0, 130.6, 129.0, 117.7, 117.5, 114.6, 113.8, 101.4, 98.7, 96.4, 81.0, 74.9, 72.7, 68.9, 67.6, 67.5, 66.6, 55.8, 55.4, 46.6, 31.8, 31.3, 25.8, 23.6, 17.5, 17.1. HRMS: $[M + Na]^+$ calculated for $C_{37}H_{51}NO_{12}Na$ 724.3309; found 724.3322.

To a solution of the above alcohol (351 mg, 0.500 mmol) in in DCM (20 mL) were added $NaHCO_3$ (840 mg, 5.00 mmol, 10 eq) and Dess-Martin periodinane (530 mg, 1.25 mmol, 2.5 eq). After stirring for 1.5 hours, 10% aq. $Na_2S_2O_3$ (20 mL) was added and the mixture was stirred for a further 30 minutes. Then, it was washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. Size-exclusion chromatography (Sephadex LH-20, eluent 1:1 DCM:MeOH) gave the title compound as a white solid (341 mg, 0.487 mmol, 97%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.32 – 7.20 (m, 2H), 7.06 – 6.99 (m, 2H), 6.92 – 6.85 (m, 2H), 6.85 – 6.76 (m, 2H), 6.16 (d, *J* = 8.2 Hz, 1H), 5.92 (ddd, *J* = 17.3, 10.6, 5.4 Hz, 1H), 5.50 (d, *J* = 3.1 Hz, 1H), 5.36 – 5.15 (m, 2H), 5.10 (t, *J* = 4.3 Hz, 1H), 5.00 (dd, *J* = 3.7, 1.7 Hz, 1H), 4.72 – 4.45 (m, 5H), 4.38 – 4.25 (m, 1H), 4.08 (dq, *J* = 13.3, 6.4 Hz, 2H), 4.03 – 3.88 (m, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 3.56 (s, 1H), 2.60 (ddd, *J* = 15.0, 8.9, 5.7 Hz, 1H), 2.41 (ddd, *J* = 15.6, 7.6, 5.5 Hz, 1H), 2.30 (ddt, *J* = 14.1, 8.9, 5.2 Hz, 1H), 2.25 – 1.99 (m, 4H), 1.84 (td, *J* = 12.7, 3.5 Hz, 1H), 1.33 (d, *J* = 6.5 Hz, 3H), 1.15 (d, *J* = 6.4 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.7, 158.9, 155.4, 154.3, 150.7, 132.7, 130.0, 128.7, 117.3, 117.2, 114.2, 113.5, 101.1, 97.6, 96.0, 80.7, 74.7, 72.1, 71.5, 69.9, 68.2, 67.1, 65.3, 55.4, 55.0, 46.2, 33.6, 31.4, 30.7, 29.1, 17.1, 17.0, 14.5. HRMS: $[M + Na]^+$ calculated for $C_{37}H_{49}NO_{12}Na$ 722.3153; found 722.3165.

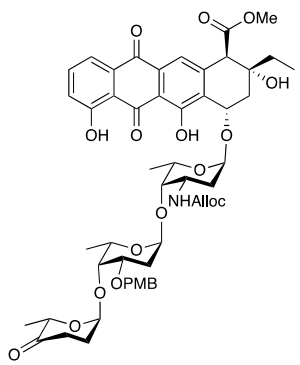
_o_-Cyclopropylethynylbenzoyl-2,3-dideoxy-4-ulo-α-L-fucopyranosyl-(1→4)-2-deoxy-3-O-_p_-methoxybenzyl-α-L-fucopyranosyl-(1→4)-3-azido-2,3-dideoxy-L-fucopyranoside (62)



To a solution of **61** (1.06 g, 1.51 mmol) in 1:1 CH_3CN:H_2O (70 mL, v/v) were added NaOAc (1.42 g, 15.1 mmol, 10 eq) and then $Ag(DPAH)_2{\cdot}H_2O$ (1.42 g, 3.10 mmol, 2.1 eq) portionwise over 30 minutes at 0°C. The mixture was stirred for 70 minutes; after which it was poured into sat. aq. $NaHCO_3$. This was then extracted with DCM thrice, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (40:60 – 60:40 EtOAc:pentane) gave the crude trisaccharide hemiacetal.

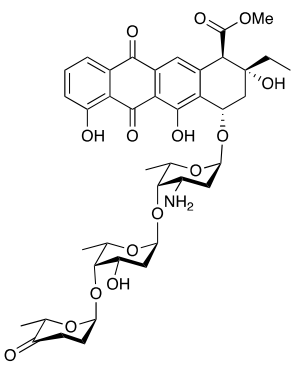
To a solution of the above crude hemiacetal in DCM (35 mL) were added DIPEA (2.42 mL, 13.6 mmol, 9 eq), DMAP (189 mg, 1.51 mmol, 1 eq), EDCI·HCl (943 mg, 4.83 mmol, 3.2 eq) and freshly saponified *o*-cyclopropylethynylbenzoic acid **43** (837 mg, 4.53 mmol, 3 eq). After stirring overnight, the mixture was diluted with DCM and washed with sat. aq. $NaHCO_3$ and brine. Drying over $MgSO_4$, concentration *in vacuo* and column chromatography of the residue (20:80 – 40:60 EtOAc:pentane) gave the title compound as a white foam (872 mg, 1.14 mmol, 75% over 2 steps, α:β 1:7). Spectral data for the β-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.94 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.48 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.42 (td, *J* = 7.5, 1.4 Hz, 1H), 7.37 – 7.16 (m, 3H), 6.93 – 6.79 (m, 2H), 6.36 (d, *J* = 8.0 Hz, 1H), 5.98 (dd, *J* = 10.0, 2.2 Hz, 1H), 5.90 (ddd, *J* = 16.3, 10.7, 5.4 Hz, 1H), 5.37 – 5.15 (m, 2H), 5.10 (t, *J* = 4.4 Hz, 1H), 5.03 – 4.97 (m, 1H), 4.75 – 4.45 (m, 5H), 4.08 (q, *J* = 6.6 Hz, 1H), 4.03 – 3.95 (m, 2H), 3.90 (ddt, *J* = 12.4, 7.4, 4.1 Hz, 1H), 3.85 – 3.78 (m, 2H), 3.76 (s, 3H), 3.49 (s, 1H), 2.60 (ddd, *J* = 15.0, 8.8, 5.7 Hz, 1H), 2.42 (ddd, *J* = 15.7, 7.7, 5.4 Hz, 1H), 2.31 (ddt, *J* = 13.9, 8.8, 5.2 Hz, 1H), 2.24 – 2.15 (m, 2H), 2.10 (tt, *J* = 10.4, 5.5 Hz, 2H), 1.81 (td, *J* = 12.3, 9.9 Hz, 1H), 1.50 (tt, *J* = 7.8, 5.4 Hz, 1H), 1.36 – 1.27 (m, 6H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.87 (dd, *J* = 7.6, 5.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.1, 164.3, 159.3, 155.8, 134.3, 132.9, 132.0, 130.3, 129.1, 127.0, 125.2, 117.7, 113.9, 101.8, 99.8, 98.0, 93.2, 80.3, 75.1, 74.5, 72.9, 72.4, 71.9, 70.3, 68.7, 65.7, 55.4, 50.0, 34.0, 32.2, 31.1, 29.5, 17.4, 14.8, 9.0, 0.8. HRMS: $[M + Na]^+$ calculated for $C_{42}H_{51}NO_{12}Na$ 784.3309; found 784.3322.

7-[2,3-Dideoxy-4-ulo-α-L-fucopyranosyl-2-deoxy-3-O-_p_-methoxybenzyl-α-L-fucopyranosyl-(1→4)-3-_N_-allyloxycarbonyl-2,3-dideoxy-α-L-fucopyranoside]-aklavinone (63)



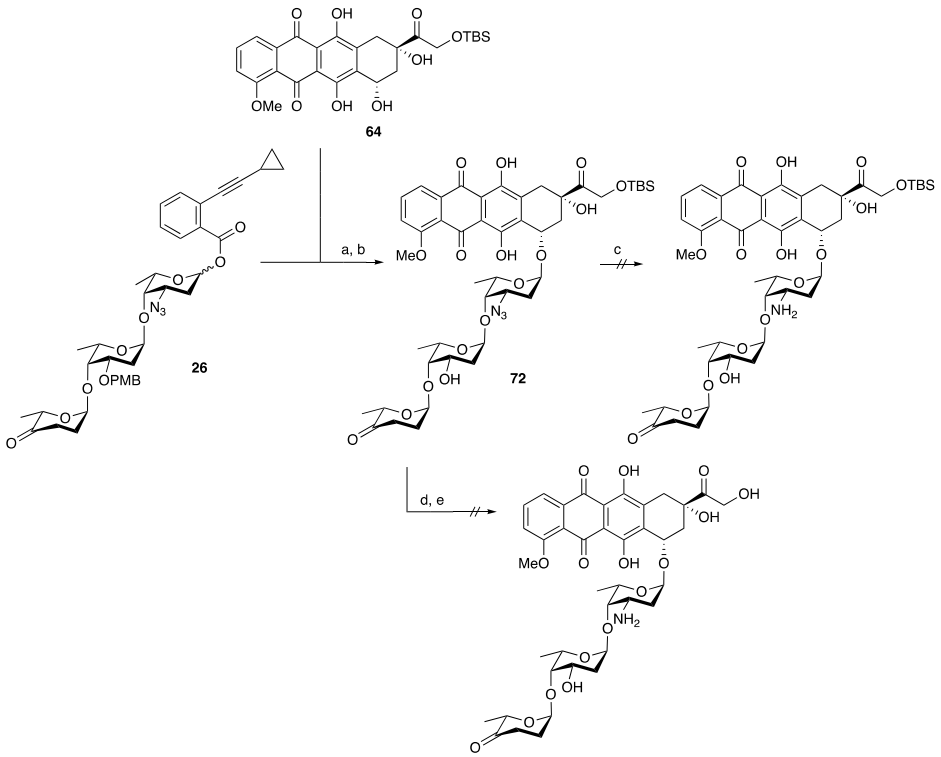
Prepared according to General Procedure C from donor **62** (211 mg, 0.276 mmol) and aklavinone **43** (2 eq) at -20°C to give after column chromatography (10:90 EtOAc:pentane and then 2:98 – 20:80 acetone:toluene) the title compound as a yellow solid (210 mg, 0.213 mmol, 77%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.66 (s, 1H), 12.01 (s, 1H), 7.82 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.72 – 7.61 (m, 2H), 7.34 – 7.21 (m, 2H), 6.93 – 6.82 (m, 2H), 6.07 (d, *J* = 7.8 Hz, 1H), 5.83 (ddt, *J* = 16.0, 10.8, 5.6 Hz, 1H), 5.46 (d, *J* = 3.8 Hz, 1H), 5.30 – 5.06 (m, 4H), 4.98 (s, 1H), 4.71 – 4.62 (m, 1H), 4.62 – 4.49 (m, 2H), 4.46 (ddt, *J* = 6.9, 5.5, 1.5 Hz, 2H), 4.22 (s, 2H), 4.12 (s, 1H), 4.09 – 3.90 (m, 3H), 3.87 (d, *J* = 7.1 Hz, 1H), 3.82 (s, 3H), 3.70 (s, 3H), 3.55 (s, 1H), 2.66 – 2.47 (m, 2H), 2.42 (ddd, *J* = 15.7, 7.6, 5.5 Hz, 1H), 2.36 – 2.25 (m, 2H), 2.25 – 2.04 (m, 3H), 2.00 (dd, *J* = 12.9, 4.5 Hz, 1H), 1.74 (dq, *J* = 13.5, 6.0, 4.3 Hz, 2H), 1.50 (dq, *J* = 14.6, 7.1 Hz, 1H), 1.30 (d, *J* = 6.6 Hz, 3H), 1.28 – 1.24 (m, 3H), 1.08 (t, *J* = 7.3 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.1, 192.8, 181.4, 171.5, 162.6, 162.2, 159.3, 155.5, 142.7, 137.4, 133.5, 133.0, 133.0, 131.1, 130.3, 129.1, 124.8, 121.0, 120.3, 117.5, 115.8, 114.8, 113.9, 101.6, 101.5, 98.0, 80.9, 75.0, 72.5, 71.8, 71.4, 70.3, 68.5, 67.7, 65.5, 57.1, 55.4, 52.6, 46.5, 34.0, 32.2, 31.6, 31.1, 29.5, 17.4, 17.3, 14.8, 6.8. HRMS: $[M + Na]^+$ calculated for $C_{52}H_{61}NO_{18}Na$ 1010.3786; found 1010.3796.

3',3'-Didesmethyl-aclarubicin (Aclacinomycin K) (10)



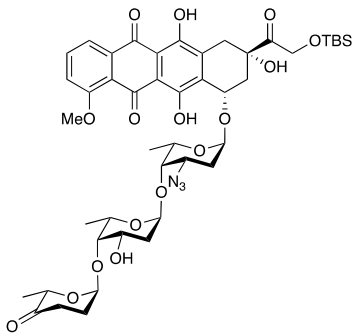
To a biphasic mixture of **63** (210 mg, 0.213 mmol) in DCM (36 mL) and phosphate buffer (3.6 mL, pH=7) was added DDQ (484 mg, 2.13 mmol, 10 eq) at 0°C after which the mixture was stirred at that temperature for 90 minutes. It was diluted with DCM, washed with H_2O four times, after which the organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography (5:95– 10:90 acetone:toluene) gave the intermediate free 3''-hydroxyl as a yellow solid (155 mg, 0.179 mmol, 84%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 12.65 (s, 1H), 12.00 (s, 1H), 7.81 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.75 – 7.60 (m, 2H), 7.32 – 7.25 (m, 1H), 6.05 (d, *J* = 7.8 Hz, 1H), 5.83 (ddt, *J* = 16.3, 10.7, 5.5 Hz, 1H), 5.46 (d, *J* = 3.8 Hz, 1H), 5.27 – 5.06 (m, 4H), 4.95 (d, *J* = 3.5 Hz, 1H), 4.53 – 4.38 (m, 3H), 4.28 – 4.18 (m, 2H), 4.18 – 4.06 (m, 3H), 3.86 (dd, *J* = 12.2, 6.5 Hz, 1H), 3.81 – 3.72 (m, 2H), 3.70 (s, 3H), 3.55 (s, 1H), 2.59 – 2.38 (m, 4H), 2.31 (d, *J* = 15.0 Hz, 1H), 2.24 – 2.06 (m, 2H), 2.01 (dd, *J* = 12.9, 4.6 Hz, 1H), 1.92 (td, *J* = 12.4, 3.8 Hz, 1H), 1.83 – 1.68 (m, 2H), 1.49 (dq, *J* = 14.7, 7.2 Hz, 1H), 1.36 – 1.24 (m, 9H), 1.08 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.9, 192.8, 181.4, 171.5, 162.6, 162.2, 155.5, 142.7, 137.4, 133.6, 133.0, 133.0, 131.1, 124.8, 121.0, 120.3, 117.5, 115.9, 114.8, 101.6, 101.6, 100.3, 82.1, 81.2, 71.9, 71.5, 71.4, 67.9, 67.7, 65.5, 65.0, 57.1, 52.6, 46.6, 34.4, 34.0, 33.5, 32.2, 31.6, 27.6, 17.3, 16.9, 14.8, 6.8. HRMS: $[M + Na]^+$ calculated for $C_{44}H_{53}NO_{17}Na$ 890.3211; found 890.3220.

A solution of the above compound (155 mg, 0.179 mmol) and *N,N*-dimethylbarbituric acid (125 mg, 0.806 mmol, 4.5 eq) in DCM (18 mL) was degassed for 5 minutes. Then, $Pd(PPh_3)_4$ (10.0 mg, 0.0090 mmol, 0.05 eq) was added and the mixture was allowed to stir for 15 minutes. It was then directly subjected to column chromatography on neutral silica (0:100 – 3:97 MeOH:DCM), followed by size-exclusion chromatography (Sephadex LH-20, eluent 1:1 DCM:MeOH) twice and finally column chromatography on neutral silica (3:97 MeOH:DCM) to give the title compound as a yellow solid (86 mg, 0.11 mmol, 61%). ^{1}H NMR (500 MHz, Chloroform-*d* + MeOD) δ 7.81 (dt, *J* = 7.4, 2.0 Hz, 1H), 7.74 – 7.62 (m, 2H), 7.30 (d, *J* = 1.2 Hz, 1H), 5.47 (t, *J* = 2.5 Hz, 1H), 5.26 (dd, *J* = 4.4, 1.8 Hz, 1H), 5.10 (t, *J* = 6.2 Hz, 1H), 4.99 (d, *J* = 3.6 Hz, 1H), 4.52 (q, *J* = 6.7 Hz, 1H), 4.19 (q, *J* = 6.7 Hz, 1H), 4.17 – 4.04 (m, 3H), 3.74 (s, 1H), 3.70 (s, 3H), 3.50 (d, *J* = 2.4 Hz, 1H), 2.99 (ddd, *J* = 10.9, 6.3, 2.4 Hz, 1H), 2.56 – 2.37 (m, 4H), 2.30 (dt, *J* = 14.9, 1.8 Hz, 2H), 2.21 – 2.12 (m, 1H), 2.09 (dd, *J* = 12.4, 4.6 Hz, 1H), 1.91 (td, *J* = 12.4, 3.8 Hz, 1H), 1.75 (ddd, *J* = 14.1, 9.4, 5.7 Hz, 3H), 1.50 (dp, *J* = 13.8, 7.0 Hz, 1H), 1.32 (d, *J* = 6.8 Hz, 3H), 1.29 (d, *J* = 6.4 Hz, 3H), 1.23 (d, *J* = 6.5 Hz, 3H), 1.08 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$ + MeOD) δ 210.3, 192.7, 181.4, 171.4, 162.4, 162.0, 142.6, 137.4, 133.5, 133.0, 131.2, 124.8, 120.9, 120.2, 115.8, 114.7, 101.6, 100.9, 100.0, 81.9, 81.8, 71.9, 71.6, 70.9, 68.1, 67.5, 65.1, 57.1, 52.6, 46.6, 34.2, 34.2, 33.8, 33.5, 32.1, 27.6, 17.4, 17.0, 14.7, 6.6. HRMS: $[M + H]^+$ calculated for $C_{40}H_{50}NO_{15}$ 784.3181; found 784.3196.



Scheme 16. Attempted synthesis of doxorubicinone trisaccharides **9** and **11** using the azide as amine protecting group. *Reagents and conditions:* (a) PPh_3AuNTf_2 (10 mol%), 4 Å MS, DCM, 95%; DDQ, DCM/pH 7 phosphate buffer (18:1, v/v), quant.; (c) PPh_3, THF/H_2O; (d) TBAF, pH 7 phosphate buffer, THF, 91%; (e) H_2S, THF/pyr. or 1,3-propanedithiol, Et_3N, DMF.

7-[2,3-Dideoxy-4-ulo-α-L-fucopyranosyl-2-deoxy-α-L-fucopyranosyl-(1→4)-3-azido-2,3-dideoxy-α-L-fucopyranoside]-14-*O*-*tert*-butyldimethylsilyl-doxorubicinone (72)

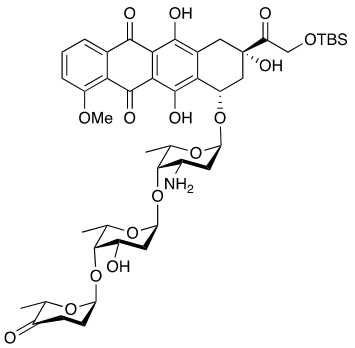


Prepared according to General Procedure C from donor **26** (226 mg, 0.322 mmol) and 14-*O*-*tert*-butyldimethylsilyl-doxorubicinone **64** (1.5 eq) to give after column chromatography (30:70 EtOAc:pentane and then 3.5:96.5 – 5:95 acetone:toluene) followed by size-exclusion chromatography (Sephadex LH-20, 1:1 DCM:MeOH v/v) the protected anthracycline trisaccharide as a red solid (320 mg, 0.306 mmol, 95%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.98 (s, 1H), 13.23 (s, 1H), 8.02 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.79 (t, *J* = 8.1 Hz, 1H), 7.41 (dd, *J* = 8.7, 1.1 Hz, 1H), 7.35 – 7.21 (m, 2H), 6.95 – 6.83 (m, 2H), 5.54 (d, *J* = 3.7 Hz, 1H), 5.29 – 5.22 (m, 1H), 5.13 – 5.01 (m, 2H), 4.87 (d, *J* = 2.2 Hz, 2H), 4.68 (q, *J* = 6.6 Hz, 1H), 4.66 – 4.49 (m, 2H), 4.41 (s, 1H), 4.25 (q, *J* = 6.6 Hz, 1H), 4.10 (s, 3H), 4.01 (q, *J* = 6.7 Hz, 1H), 3.96 (d, *J* = 2.7 Hz, 1H), 3.90 (ddd, *J* = 9.8, 7.2, 2.6 Hz, 1H), 3.83 (s, 3H), 3.77 – 3.66 (m, 2H), 3.28 – 2.88 (m, 2H), 2.62 (ddd, *J* = 15.2, 9.0, 5.8 Hz, 1H), 2.41 (ddd, *J* = 15.6, 7.4, 5.5 Hz, 1H), 2.34 – 2.14 (m, 4H), 2.14 – 2.05 (m, 2H), 1.97 (td, *J* = 12.8, 4.0 Hz, 1H), 1.81 (dd, *J* = 12.9, 4.4 Hz, 1H), 1.28 (d, *J* = 6.5 Hz, 3H), 1.25 (d, *J* = 6.5 Hz, 4H), 1.00 – 0.94 (m, 13H), 0.15 (d, *J* = 1.5 Hz, 7H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.3, 211.1, 187.2, 186.8, 161.2, 159.3, 156.4, 155.8, 135.9, 135.6, 134.0, 133.7, 130.4, 129.2, 120.9, 120.0, 118.6, 113.9, 111.6, 111.5, 100.8,

99.6, 98.0, 75.3, 74.4, 72.6, 71.8, 70.2, 70.1, 68.1, 66.8, 56.8, 56.7, 55.4, 35.7, 34.1, 30.6, 29.7, 26.0, 18.7, 17.7, 17.6, 14.9. HRMS: $[M + Na]^+$ calculated for $C_{53}H_{67}N_3O_{17}SiNa$ 1068.4137; found 1068.4141.

To a biphasic mixture of the above compound (226 mg, 0.216 mmol) in DCM (36 mL) and phosphate buffer (2 mL, pH=7) was added DDQ (53.9 mg, 0.24 mmol, 1.1 eq) at 0°C after which the mixture was stirred at that temperature for 2.5 hours. Then, the same amount of DDQ was added and the mixture was stirred for a further 3 hours. It was diluted with DCM, washed with H_2O four times, after which the organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography (3.5:96.5 – 8:92 – 20:80 acetone:toluene) gave the title compound as a red solid (158 mg, 0.171 mmol, 79%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.92 (s, 1H), 13.17 (s, 1H), 8.06 – 7.93 (m, 1H), 7.78 (t, *J* = 8.1 Hz, 1H), 7.49 – 7.35 (m, 1H), 5.54 (d, *J* = 3.7 Hz, 1H), 5.31 – 5.17 (m, 1H), 5.17 – 5.07 (m, 1H), 5.03 (d, *J* = 3.6 Hz, 1H), 4.95 – 4.79 (m, 2H), 4.50 (q, *J* = 6.7 Hz, 1H), 4.43 – 4.31 (m, 2H), 4.16 – 4.05 (m, 4H), 4.01 (q, *J* = 6.4 Hz, 1H), 3.80 – 3.63 (m, 4H), 3.28 – 2.82 (m, 2H), 2.55 – 2.37 (m, 3H), 2.29 (d, *J* = 15.2 Hz, 1H), 2.24 – 2.07 (m, 3H), 2.02 (td, *J* = 12.9, 12.4, 3.8 Hz, 1H), 1.85 (ddt, *J* = 17.3, 9.5, 4.2 Hz, 2H), 1.35 – 1.18 (m, 9H), 0.96 (s, 9H), 0.15 (d, *J* = 1.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.0, 210.2, 187.0, 186.7, 161.1, 156.3, 155.7, 135.9, 135.5, 133.9, 133.7, 120.8, 119.9, 118.6, 111.5, 111.4, 100.8, 100.3, 99.9, 82.7, 75.0, 71.9, 70.1, 67.9, 67.4, 66.7, 65.3, 56.8, 56.8, 34.0, 33.9, 33.6, 29.6, 27.6, 26.0, 18.7, 17.6, 17.1, 14.9. HRMS: $[M + Na]^+$ calculated for $C_{45}H_{59}N_3O_{16}SiNa$ 948.3562; found 948.3564.

7-[2,3-Dideoxy-4-ulo-α-L-fucopyranosyl-2-deoxy-α-L-fucopyranosyl-(1→4)-3-amino-2,3-dideoxy-α-L-fucopyranoside]-14-*O*-*tert*-butyldimethylsilyl-doxorubicinone (65)



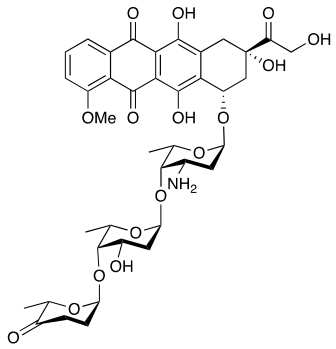
Prepared according to General Procedure C from donor **62** (422 mg, 0.552 mmol) and doxorubicinone acceptor **64** (Chapter 2) (1.5 eq) to give after column chromatography (20:80 – 100:0 EtOAc:pentane) the crude anthracycline trisaccharide.

To a solution of the above trisaccharide in DCM (93 mL) and phosphate buffer (9.3 mL, pH=7) was added DDQ (1.25 g, 5.52 mmol, 10 eq) at 0°C after which the mixture was stirred at that temperature for 45 minutes. It was then stirred at room temperature for an additional 2.5 hours, after which it was diluted with DCM and washed with H_2O four times. The organic layer was then dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography (5:95– 12:88 acetone:toluene) gave the free 3''-hydroxyl anthracycline trisaccharide as a red solid (310 mg, 0.315 mmol, 57% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.93 (s, 1H), 13.24 (s, 1H), 8.03 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.78 (t, *J* = 8.1 Hz, 1H), 7.39 (dd, *J* = 8.6, 1.1 Hz, 1H), 6.02 (d, *J* = 7.9 Hz, 1H), 5.84 (ddt, *J* = 16.2, 10.8, 5.5 Hz, 1H), 5.51 (d, *J* = 3.7 Hz, 1H), 5.26 (td, *J* = 3.4, 1.7 Hz, 1H), 5.23 – 5.05 (m, 2H), 4.99 – 4.93 (m, 1H), 4.90 (d, *J* = 2.8 Hz, 2H), 4.58 – 4.41 (m, 4H), 4.19 – 4.10 (m, 3H), 4.09 (s, 3H), 3.93 – 3.82 (m, 1H), 3.78 – 3.70 (m, 2H), 3.58 (s, 1H), 3.20 (dd, *J* = 18.7, 1.8 Hz, 1H), 2.97 (d, *J* = 18.9 Hz, 1H), 2.55 – 2.39 (m, 3H), 2.29 (d, *J* = 14.8 Hz, 1H), 2.24 – 2.02 (m, 4H), 1.92 (ddd, *J* = 14.0, 10.0, 3.8 Hz, 2H), 1.83 – 1.72 (m, 1H), 1.37 – 1.22 (m, 10H), 0.96 (s, 9H), 0.14 (d, *J* = 2.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.5, 209.9, 187.2, 186.8, 161.1, 156.5, 156.0, 155.6, 135.8, 135.6, 134.2, 134.0, 133.0, 121.0, 119.9, 118.5, 117.6, 111.6, 111.4, 101.6, 100.9, 100.3, 82.2, 81.1, 72.0, 69.8, 67.9, 66.8, 65.6, 65.0, 56.8, 46.6, 35.8, 34.4, 34.2, 33.5, 31.4, 27.6, 26.0, 18.7, 17.5, 16.9, 14.9. HRMS: $[M + Na]^+$ calculated for $C_{49}H_{65}NO_{18}SiNa$ 1006.3869; found 1006.3876.

A solution of the above compound (159 mg, 0.162 mmol) and *N,N*-dimethylbarbituric acid (115 mg, 0.729 mmol, 4.5 eq) in DCM (16.3 mL) was degassed for 5 minutes. Then, $Pd(PPh_3)_4$ (9.0 mg, 81 µmol, 0.05 eq) was added and the mixture was allowed to stir for 20 minutes. It was then directly subjected to column chromatography on neutral silica (0:100 – 3:97 MeOH:DCM) to give the title compound as a red solid (118 mg, 0.131 mmol, 81%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 13.90 (s, 1H), 7.97 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.75 (t, *J* = 8.1 Hz, 1H), 7.38 (dd, *J* = 8.7, 1.1 Hz, 1H), 5.48 (d, *J* = 3.7 Hz, 1H), 5.23 (dd, *J* = 4.1, 2.2 Hz, 1H), 5.10 (t, *J* = 6.1 Hz, 1H), 5.01 (d, *J* = 3.6 Hz, 1H), 4.94 – 4.81 (m, 2H), 4.50 (q, *J* = 6.7 Hz, 1H), 4.25 (q, *J* = 6.6 Hz, 1H), 4.13 (ddd, *J* = 12.2, 4.7, 2.7 Hz, 1H), 4.08 (s, 3H), 4.03 (q, *J* = 6.4 Hz, 1H), 3.73 (s, 1H), 3.52 (d, *J* = 2.5 Hz, 1H), 3.13 (dd, *J* = 18.8, 1.9 Hz, 1H), 3.00 (ddd, *J* = 12.4, 4.7, 2.4 Hz, 1H), 2.89 (d, *J* = 18.7 Hz, 1H), 2.56 – 2.38 (m, 3H), 2.30 (dt, *J* = 14.8, 2.1 Hz, 1H), 2.23 – 2.00 (m, 3H), 1.89 (td, *J* = 12.4, 3.8 Hz, 1H), 1.75 (td, *J* = 12.9, 3.9 Hz, 1H), 1.68 (dd, *J* = 13.1, 4.5 Hz, 1H), 1.33 (d, *J* = 6.8 Hz, 3H), 1.28 (d, *J* = 6.5 Hz, 3H), 1.22 (d, *J* = 6.5 Hz, 3H), 0.96 (s, 9H), 0.14 (d, *J* = 1.2 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.2, 210.0, 186.9, 186.6, 161.1,

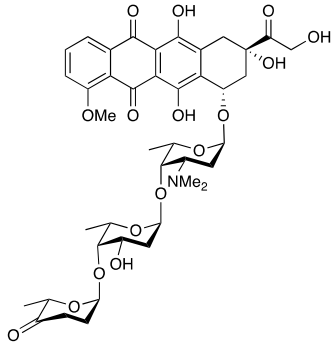
156.4, 155.8, 135.7, 135.5, 134.1, 120.8, 119.8, 118.5, 111.4, 101.4, 100.8, 100.2, 82.3, 81.7, 71.9, 69.6, 68.4, 67.4, 66.6, 65.2, 56.7, 46.8, 35.6, 34.4, 33.9, 33.5, 27.7, 26.0, 18.7, 17.7, 17.2, 14.8. HRMS: $[M + H]^+$ calculated for $C_{45}H_{62}NO_{16}Si$ 900.3838; found 900.3836.

7-[2,3-Dideoxy-4-ulo-α-L-fucopyranosyl-2-deoxy-α-L-fucopyranosyl-(1→4)-3-amino-2,3-dideoxy-α-L-fucopyranoside]-doxorubicinone (9)



To a solution of **65** (19.7 mg, 21.9 µmol) in pyridine (0.7 mL) and THF (1.4 mL) in a PTFE tube, was added HF.pyr complex (70 wt% HF, 86 µL) at 0°C. After 3 hours, an additional such portion of HF.pyr complex was added. After stirring one more hour, solid $NaHCO_3$ was added to quench and the mixture was stirred until cessation of effervescence. It was then filtered off, and the filtrate was poured into DCM/H_2O. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography on neutral silica (DCM – 4:96 MeOH:DCM) gave the title compound as a red solid (12.7 mg, 16.2 µmol, 74%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 13.94 (s, 1H), 8.13 – 7.89 (m, 1H), 7.78 (t, *J* = 8.1 Hz, 1H), 7.52 – 7.31 (m, 1H), 5.51 (d, *J* = 3.8 Hz, 1H), 5.36 – 5.27 (m, 1H), 5.09 (t, *J* = 6.1 Hz, 1H), 5.01 (d, *J* = 3.7 Hz, 1H), 4.81 – 4.68 (m, 2H), 4.49 (q, *J* = 6.6 Hz, 1H), 4.23 (q, *J* = 6.4 Hz, 1H), 4.16 – 4.05 (m, 4H), 4.01 (q, *J* = 6.5 Hz, 1H), 3.72 (s, 1H), 3.52 (s, 1H), 3.25 (dd, *J* = 18.9, 2.0 Hz, 1H), 3.08 – 2.96 (m, 2H), 2.46 (dtt, *J* = 17.8, 10.3, 5.8 Hz, 4H), 2.32 (dt, *J* = 14.5, 2.1 Hz, 1H), 2.25 (t, *J* = 7.6 Hz, 1H), 2.22 – 2.05 (m, 4H), 1.89 (td, *J* = 12.3, 3.7 Hz, 1H), 1.76 (td, *J* = 12.9, 3.9 Hz, 1H), 1.70 (d, *J* = 4.5 Hz, 1H), 1.33 (d, *J* = 6.5 Hz, 3H), 1.28 (d, *J* = 6.4 Hz, 3H), 1.22 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.9, 210.0, 187.2, 186.8, 161.2, 156.4, 155.8, 135.9, 135.6, 134.0, 133.7, 121.0, 120.0, 118.6, 111.7, 111.5, 101.3, 100.9, 100.3, 82.4, 81.7, 72.0, 69.2, 68.5, 67.5, 65.6, 65.3, 56.8, 46.8, 35.6, 34.5, 34.1, 33.6, 27.7, 17.8, 17.2, 14.9. HRMS: $[M + H]^+$ calculated for $C_{39}H_{48}NO_{16}$: 786.2973; found 786.2982.

7-[2,3-Dideoxy-4-ulo-α-L-fucopyranosyl-2-deoxy-α-L-fucopyranosyl-(1→4)-3-dimethylamino-2,3-dideoxy-α-L-fucopyranoside]-doxorubicinone (11)

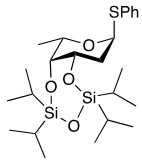


To a solution of **65** (48.0 mg, 53.3 µmol) in EtOH (10.8 mL) and 37% aq. CH_2O (132 µL, 30 eq) was added $NaBH(OAc)_3$ (21.5 mg, 0.101 mmol, 1.9 eq). The mixture was stirred for 1.5 hours before being poured into sat. aq. $NaHCO_3$. This was repetitively extracted with DCM, dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography on neutral silica (10:90 – 40:60 acetone:toluene) followed by size-exclusion chromatography (Sephadex LH-20, 1:1 DCM:MeOH v/v) gave the free amine as a red solid (25.8 mg, 27.8 µmol, 52%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 13.93 (s, 1H), 13.24 (s, 1H), 8.01 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.83 – 7.70 (m, 1H), 7.45 – 7.36 (m, 1H), 5.53 (d, *J* = 3.8 Hz, 1H), 5.26 (dd, *J* = 4.1, 2.1 Hz, 1H), 5.10 – 5.06 (m, 1H), 5.03 (d, *J* = 3.4 Hz, 1H), 4.97 – 4.82 (m, 2H), 4.77 (s, 1H), 4.55 (q, *J* = 6.4 Hz, 1H), 4.50 (q, *J* = 6.7 Hz, 1H), 4.09 (d, *J* = 3.3 Hz, 4H), 3.92 (q, *J* = 6.6 Hz, 1H), 3.75 (s, 1H), 3.72 – 3.58 (m, 2H), 3.18 (dd, *J* = 18.9, 2.0 Hz, 1H), 2.98 (d, *J* = 18.8 Hz, 1H), 2.53 – 2.38 (m, 3H), 2.32 (dt, *J* = 14.6, 2.2 Hz, 1H), 2.26 – 2.01 (m, 10H), 1.94 – 1.73 (m, 4H), 1.33 (d, *J* = 6.8 Hz, 3H), 1.31 – 1.20 (m, 7H), 1.17 (d, *J* = 6.4 Hz, 3H), 0.96 (s, 9H), 0.14 (d, *J* = 2.8 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.4, 210.3, 187.1, 186.7, 161.1, 156.6, 155.9, 135.8, 135.6, 134.3, 134.1, 124.9, 121.0, 119.9, 118.5, 111.5, 111.4, 101.5, 100.3, 99.6, 83.1, 74.1, 71.9, 69.7, 68.6, 66.7, 65.4, 61.7, 56.8, 43.4, 35.6, 34.4, 34.0, 33.6, 30.4, 29.8, 27.7, 26.0, 18.1, 17.1, 14.9. HRMS: $[M + H]^+$ calculated for $C_{47}H_{66}NO_{16}Si$: 928.4151; found 928.4157.

To a solution of the above compound (20.6 mg, 22.2 µmol) in pyridine (1.4 mL) and THF (1.4 mL) in a PTFE tube, was added HF.pyr complex (70 wt% HF, 87 µL) at 0°C. Four more additional such amounts of HF.pyr complex were added over the course of 4.5 hours. Then, solid $NaHCO_3$ was added to quench and the mixture was stirred until cessation of effervescence. It was then filtered off, and the filtrate was poured into DCM/H_2O. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography on neutral silica (DCM – 10:90 MeOH:DCM) gave the title compound as a red solid (13.3 mg, 16.3 µmol, 73%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 13.95 (s, 1H), 13.26 (s,

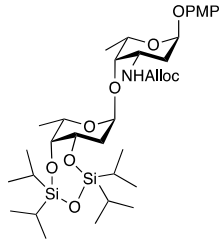
1H), 8.03 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.79 (dd, *J* = 8.5, 7.7 Hz, 1H), 7.40 (dd, *J* = 8.7, 1.1 Hz, 1H), 5.55 (d, *J* = 3.8 Hz, 1H), 5.32 – 5.28 (m, 1H), 5.08 (dd, *J* = 7.0, 5.6 Hz, 1H), 5.03 (s, 1H), 4.92 (s, 1H), 4.76 (d, *J* = 1.0 Hz, 2H), 4.54 (d, *J* = 6.6 Hz, 1H), 4.49 (q, *J* = 6.7 Hz, 1H), 4.16 – 4.03 (m, 4H), 3.91 (q, *J* = 6.5 Hz, 1H), 3.76 (s, 1H), 3.71 – 3.60 (m, 2H), 3.26 (dd, *J* = 18.8, 2.0 Hz, 1H), 3.03 (d, *J* = 18.8 Hz, 1H), 2.54 – 2.40 (m, 3H), 2.34 (dt, *J* = 14.6, 2.2 Hz, 1H), 2.24 – 2.12 (m, 7H), 2.10 (dd, *J* = 12.1, 4.6 Hz, 1H), 2.03 (d, *J* = 15.0 Hz, 1H), 1.83 (td, *J* = 12.2, 3.8 Hz, 3H), 1.33 (d, *J* = 6.7 Hz, 3H), 1.27 (d, *J* = 6.6 Hz, 3H), 1.17 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.9, 210.3, 187.3, 186.9, 161.2, 156.5, 155.9, 135.9, 135.6, 134.2, 133.7, 121.1, 119.9, 118.5, 111.7, 111.5, 101.4, 100.3, 99.6, 83.1, 74.1, 71.9, 69.3, 68.8, 66.9, 65.6, 65.4, 61.8, 56.8, 43.5, 35.6, 34.4, 34.1, 33.7, 27.8, 18.2, 17.1, 14.9. HRMS: $[M + H]^+$ calculated for $C_{41}H_{52}NO_{16}$: 814.3286; found 814.3301.

Phenyl 2-deoxy-3,4-tetraisopropyldisiloxyl-1-thio-α-L-fucopyranoside (66)



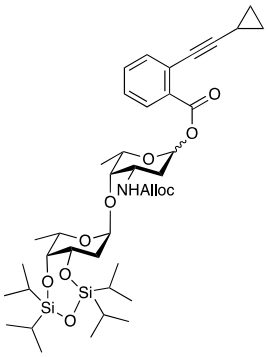
A solution of **34** (6.35 g, 19.6 mmol) and NaOMe (cat. amount) in MeOH (200 mL) was stirred overnight. It was then quenched by addition of Amberlite IR120 (H^+ form), filtered and concentrated *in vacuo* to give the intermediate diol. To a solution of this diol in pyridine (100 mL) was added tetraisopropyldisiloxane dichloride (8.3 mL, 25.5 mmol, 1.3 eq) and the resulting mixture was stirred overnight. It was then poured into Et_2O, washed with H_2O thrice and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (4:96 – 8:92 toluene:pentane) gave the title compound as a colourless oil (6.36 g, 13.2 mmol, 67%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.52 – 7.38 (m, 2H), 7.34 – 7.13 (m, 3H), 5.69 (d, *J* = 5.6 Hz, 1H), 4.38 – 4.34 (m, 1H), 4.34 – 4.29 (m, 1H), 4.07 – 3.92 (m, 1H), 2.45 (td, *J* = 12.7, 5.8 Hz, 1H), 2.00 (ddt, *J* = 13.0, 4.6, 1.1 Hz, 1H), 1.26 (d, *J* = 6.4 Hz, 3H), 1.14 – 0.86 (m, 28H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.8, 130.8, 129.0, 126.8, 84.6, 73.4, 71.4, 67.7, 34.1, 17.8, 17.8, 17.7, 17.6, 17.5, 17.5, 17.4, 17.3, 14.4, 14.2, 13.2, 12.7. HRMS: $[M + Na]^+$ calculated for $C_{24}H_{42}O_4SSi_2Na$ 505.2240; found 505.2238.

***p*-Methoxyphenyl-2-deoxy-3,4-tetraisopropyldisiloxyl-α-L-fucopyranosyl-(1→4)-3-*N*-allyloxycarbonyl-2,3-dideoxy-α-L-fucopyranoside (67)**



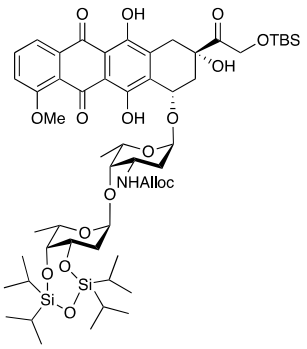
To a solution of the glycosyl acceptor **41** (901 mg, 2.67 mmol, 1 eq) and the glycosyl donor **66** (1.80 g, 3.73 mmol, 1.3 eq) in Et_2O:DCE (70 mL, 4:1 v/v), activated molecular sieves (4Å) were added. The mixture was stirred for 30 minutes and then, at 10°C, iodonium dicollidine perchlorate (5.00 mg, 10.7 mmol, 4 eq) was added. After 30 minutes, triphenylphosphine (1.40 g, 5.34 mmol, 2 eq) was added and the mixture was stirred for an additional hour. It was then diluted with EtOAc and filtered, washed with 10% aq. $Na_2S_2O_3$, 1M $CuSO_4$ solution twice, H_2O and then dried over $MgSO_4$. Concentration *in vacuo* and column chromatography (5:95 – 10:90 EtOAc:pentane) of the residue gave the title compound as a white foam (1.69 g, 2.38 mmol, 89%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.05 – 6.93 (m, 2H), 6.93 – 6.70 (m, 2H), 6.16 (d, *J* = 7.9 Hz, 1H), 5.92 (ddt, *J* = 16.1, 10.9, 5.6 Hz, 1H), 5.52 (d, *J* = 3.2 Hz, 1H), 5.30 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.20 (dq, *J* = 10.5, 1.4 Hz, 1H), 4.93 (d, *J* = 3.7 Hz, 1H), 4.58 (qdt, *J* = 13.3, 5.6, 1.4 Hz, 2H), 4.41 (ddd, *J* = 12.2, 4.6, 2.5 Hz, 1H), 4.37 – 4.25 (m, 1H), 4.14 – 4.04 (m, 2H), 4.01 (s, 1H), 3.77 (s, 3H), 3.54 (s, 1H), 2.19 – 2.05 (m, 2H), 1.99 (dd, *J* = 12.6, 4.6 Hz, 1H), 1.89 (td, *J* = 12.7, 3.5 Hz, 1H), 1.34 (d, *J* = 6.4 Hz, 3H), 1.18 (d, *J* = 6.5 Hz, 3H), 1.14 – 0.83 (m, 28H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.6, 154.4, 150.9, 132.8, 117.4, 117.2, 114.4, 101.8, 96.2, 81.2, 73.0, 69.8, 68.0, 67.4, 65.4, 55.5, 46.4, 33.1, 31.5, 17.6, 17.5, 17.4, 17.3, 17.3, 17.2, 17.2, 17.2, 17.1, 17.1, 14.1, 13.9, 13.0, 12.4. HRMS: $[M + Na]^+$ calculated for $C_{35}H_{59}NO_{10}Si_2Na$ 732.35752; found 732.3587.

_o_-Cyclopropylethynylbenzoyl-2-deoxy-3,4-tetraisopropyldisiloxane-α-L-fucopyranosyl-(1→4)-3-N-allyloxycarbonyl-2,3-dideoxy-L-fucopyranoside (68)



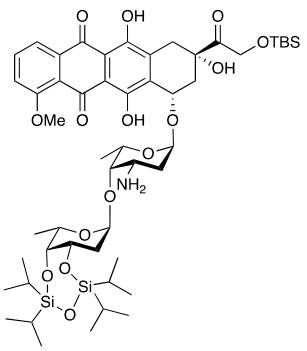
Prepared according to General Procedure A and B from **67** (1.69 g, 2.38 mmol) to give after column chromatography (10:90 – 20:80 EtOAc:pentane) the title compound as a white foam (1.54 g, 1.99 mmol, 84% over 2 steps, α:β 1:8). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.00 – 7.85 (m, 1H), 7.47 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.41 (ddd, *J* = 9.1, 6.0, 1.4 Hz, 1H), 7.35 – 7.24 (m, 1H), 6.35 (d, *J* = 7.6 Hz, 1H), 5.99 (dd, *J* = 10.0, 2.3 Hz, 1H), 5.96 – 5.84 (m, 1H), 5.36 – 5.15 (m, 2H), 4.93 (d, *J* = 3.9 Hz, 1H), 4.56 (qdt, *J* = 13.3, 5.6, 1.5 Hz, 2H), 4.45 (ddd, *J* = 12.1, 4.5, 2.5 Hz, 1H), 4.11 – 4.06 (m, 1H), 4.01 (d, *J* = 2.5 Hz, 1H), 3.87 (dddd, *J* = 12.1, 7.1, 4.1, 2.6 Hz, 1H), 3.85 – 3.79 (m, 1H), 3.48 – 3.44 (m, 1H), 2.22 (ddd, *J* = 11.9, 4.1, 2.2 Hz, 1H), 2.14 (td, *J* = 12.4, 4.0 Hz, 1H), 1.99 (dd, *J* = 12.4, 4.6 Hz, 1H), 1.85 (td, *J* = 12.3, 10.0 Hz, 1H), 1.51 (tt, *J* = 7.2, 5.7 Hz, 1H), 1.36 – 1.30 (m, 6H), 1.13 – 0.81 (m, 28H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.3, 155.8, 134.2, 133.0, 132.0, 131.1, 130.8, 127.0, 125.1, 117.7, 102.3, 99.8, 93.2, 80.6, 74.5, 73.3, 73.0, 69.9, 68.4, 65.7, 50.1, 33.3, 32.2, 17.8, 17.8, 17.6, 17.5, 17.5, 17.5, 17.4, 17.3, 14.3, 14.2, 13.2, 12.7, 9.0, 8.9, 0.8. HRMS: $[M + Na]^+$ calculated for $C_{40}H_{61}NO_{10}Si_2Na$ 794.37317; found 794.3749.

7-[2-Deoxy-3,4-tetraisopropyldisiloxyl-α-L-fucopyranosyl-(1→4)-3-*N*-allyloxycarbonyl-2,3-dideoxy-α-L-fucopyranoside]-14-*O*-*tert*-butyldimethylsilyl-doxorubicinone (69)



Prepared according to General Procedure C from donor **68** (722 mg, 1.00 mmol) and 14-*O*-*tert*-butyldimethylsilyl-doxorubicinone **64** (793 mg, 1.50 mmol, 1.5 eq) to give after column chromatography (5:95 – 20:80 EtOAc:pentane – 4:96 acetone:toluene) the title compound as a red solid (714 mg, 0.640 mmol, 64%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 13.83 (s, 1H), 13.09 (s, 1H), 7.93 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.72 (t, *J* = 8.1 Hz, 1H), 7.43 – 7.32 (m, 1H), 6.07 (d, *J* = 7.8 Hz, 1H), 5.91 – 5.78 (m, 1H), 5.50 (d, *J* = 3.8 Hz, 1H), 5.27 – 5.18 (m, 2H), 5.13 (dq, *J* = 10.5, 1.4 Hz, 1H), 4.98 – 4.86 (m, 3H), 4.61 – 4.37 (m, 4H), 4.13 (q, *J* = 6.5 Hz, 1H), 4.05 (d, *J* = 24.2 Hz, 6H), 3.90 – 3.77 (m, 1H), 3.55 (s, 1H), 3.09 (dd, *J* = 18.8, 2.0 Hz, 1H), 2.81 (d, *J* = 18.7 Hz, 1H), 2.29 (d, *J* = 14.6 Hz, 1H), 2.22 – 2.05 (m, 2H), 2.05 – 1.95 (m, 1H), 1.92 (dd, *J* = 13.1, 4.5 Hz, 1H), 1.78 (td, *J* = 12.9, 4.0 Hz, 1H), 1.30 (dd, *J* = 16.4, 6.4 Hz, 6H), 1.16 – 0.82 (m, 37H), 0.15 (d, *J* = 2.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.4, 186.8, 186.4, 161.0, 156.3, 155.7, 135.7, 135.3, 134.0, 133.9, 132.9, 120.7, 119.8, 118.5, 117.5, 111.3, 111.2, 101.9, 101.0, 81.0, 73.2, 69.9, 69.7, 68.2, 68.0, 66.7, 65.5, 56.7, 46.6, 35.7, 34.0, 33.3, 31.3, 26.0, 18.7, 17.8, 17.7, 17.6, 17.5, 17.5, 17.5, 17.4, 17.3, 17.2, 14.3, 14.1, 13.1, 12.6, -5.2, -5.3. HRMS: $[M + Na]^+$ calculated for $C_{55}H_{83}NO_{17}Si_3Na$ 1136.48665; found 1136.4866.

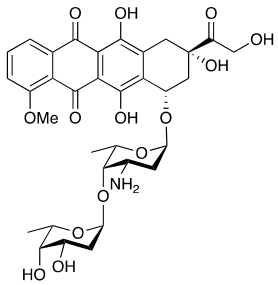
7-[2-Deoxy-3,4-tetraisopropyldisiloxyl-α-L-fucopyranosyl-(1→4)-3-amino-2,3-dideoxy-α-L-fucopyranoside]-14-*O*-*tert*-butyldimethylsilyl-doxorubicinone (70)



A solution of **69** (704 mg, 0.631 mmol) and *N*,*N*-dimethylbarbituric acid (440 mg, 2.84 mmol, 4.5 eq) in DCM (63 mL) was degassed for 5 minutes. Then, $Pd(PPh_3)_4$ (36.5 mg, 0.032 mmol, 0.05 eq) was added and the mixture was allowed to stir for 20 minutes. It was then directly subjected to column chromatography (pentane, then 0:100 – 50:50 acetone:toluene) to give the title compound as a red solid (650 mg, 0.631 mmol, 100%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.93 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.73 (t, *J* = 8.1 Hz, 1H), 7.42 – 7.33 (m, 1H), 5.53 – 5.41 (m, 1H), 5.21 (dd, *J* = 4.1, 2.2 Hz, 1H), 4.98 (d, *J* = 3.7 Hz, 1H), 4.96 – 4.81 (m, 2H), 4.65 (s, 1H), 4.42 (ddd, *J* = 12.1, 4.6, 2.5 Hz, 1H), 4.15 (q, *J* = 6.5 Hz, 1H), 4.10 – 3.93 (m, 5H), 3.53 (s, 1H), 3.40 – 3.20 (m, 3H), 3.18 – 3.00 (m, 2H), 2.82 (d, *J* = 18.7 Hz, 1H), 2.29 (dt, *J* = 14.8, 2.2 Hz, 1H), 2.21 – 2.09 (m, 2H), 2.05 – 1.93 (m, 1H), 1.76 (ddd, *J* = 27.6,

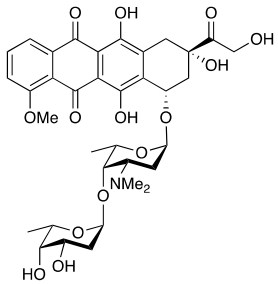
14.0, 4.2 Hz, 1H), 1.29 (d, *J* = 6.5 Hz, 3H), 1.23 (d, *J* = 6.5 Hz, 3H), 1.13 – 0.75 (m, 36H), 0.15 (d, *J* = 1.4 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.2, 186.7, 186.4, 161.0, 156.3, 155.6, 135.7, 135.3, 134.0, 132.1, 132.1, 128.6, 120.7, 119.7, 118.5, 111.3, 101.3, 101.1, 81.5, 73.3, 70.1, 69.6, 68.3, 67.8, 66.6, 56.7, 46.8, 35.6, 33.8, 33.4, 25.9, 18.7, 17.7, 17.7, 17.6, 17.6, 17.5, 17.5, 17.4, 17.3, 17.2, 14.2, 14.1, 13.1, 12.6. HRMS: $[M + H]^+$ calculated for $C_{51}H_{80}NO_{15}Si_3$ 1030.48358; found 1030.4855.

7-[2-Deoxy-α-L-fucopyranosyl-(1→4)-3-amino-2,3-dideoxy-α-L-fucopyranoside]- doxorubicinone (5)



To a solution of **70** (30.5 mg, 29.6 μmol) in pyridine (3.0 mL) in a PTFE tube, was added HF.pyr complex (70 wt% HF, 232 μL) at 0 °C. Over the course of 4 hours, 2 additional such portions of HF.pyr complex were added. Then, solid $NaHCO_3$ was added to quench and the mixture was stirred until cessation of effervescence. It was then filtered off and concentrated *in vacuo*. Column chromatography on neutral silica (0:100 – 20:80 MeOH:DCM) gave the title compound as a red solid (15.1 mg, 22.4 μmol, 76%). ^{1}H NMR (500 MHz, Pyridine-d_5) δ 7.78 (d, *J* = 7.7 Hz, 1H), 7.46 (t, *J* = 8.1 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 5.52 (d, *J* = 3.0 Hz, 1H), 5.17 (d, *J* = 3.9 Hz, 1H), 5.12 (d, *J* = 2.3 Hz, 2H), 5.06 (d, *J* = 3.8 Hz, 1H), 4.36 (dt, *J* = 12.1, 3.9 Hz, 1H), 4.33 – 4.19 (m, 2H), 3.80 (d, *J* = 2.9 Hz, 1H), 3.68 (s, 3H), 3.54 (s, 1H), 3.41 (t, *J* = 8.7 Hz, 1H), 3.34 – 3.12 (m, 2H), 2.51 (d, *J* = 14.4 Hz, 1H), 2.30 (td, *J* = 12.2, 3.9 Hz, 1H), 2.22 (dd, *J* = 14.3, 5.1 Hz, 1H), 2.08 (dd, *J* = 12.3, 4.9 Hz, 1H), 1.97 (dd, *J* = 9.2, 2.8 Hz, 2H), 1.27 (d, *J* = 6.4 Hz, 3H), 1.06 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, Pyr) δ 215.4, 187.5, 161.9, 157.5, 156.2, 135.2, 121.6, 120.1, 119.9, 112.3, 112.0, 101.9, 101.9, 81.6, 77.1, 72.4, 70.9, 69.0, 68.8, 66.7, 66.2, 57.1, 48.0, 37.9, 34.6, 34.4, 34.2, 18.1. HRMS: $[M + H]^+$ calculated for $C_{33}H_{40}NO_{14}$ 674.24488; found 674.2456.

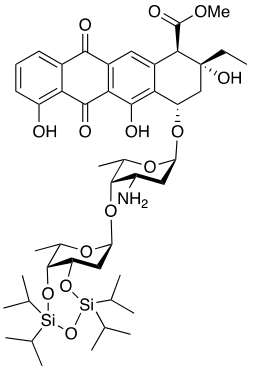
7-[2-Deoxy-α-L-fucopyranosyl-(1→4)-3-dimethylamino-2,3-dideoxy-α-L-fucopyranoside]-doxorubicinone (7)



To a solution of **70** (102 mg, 99 μmol) in EtOH (20 mL) and 37% aq. CH_2O (245 μL, 30 eq) was added $NaBH(OAc)_3$ (40 mg, 0.193 mmol, 1.95 eq). The mixture was stirred for 1.5 hours before being poured into sat. aq. $NaHCO_3$. This was extracted with DCM, dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography chromatography (3:97 acetone:toluene) gave the dimethylated amine as a red solid (75 mg, 70.9 μmol, 71%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 13.92 (s, 1H), 13.24 (s, 1H), 8.01 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.77 (t, *J* = 8.1 Hz, 1H), 7.43 – 7.37 (m, 1H), 5.54 (d, *J* = 3.8 Hz, 1H), 5.25 (dd, *J* = 4.1, 2.1 Hz, 1H), 5.01 (d, *J* = 3.4 Hz, 1H), 4.98 – 4.84 (m, 2H), 4.79 (s, 1H), 4.49 – 4.34 (m, 2H), 4.09 (s, 3H), 3.95 (t, *J* = 1.8 Hz, 1H), 3.91 (q, *J* = 6.5 Hz, 1H), 3.75 (s, 1H), 3.38 – 3.35 (m, 1H), 3.18 (dd, *J* = 18.9, 1.9 Hz, 1H), 2.98 (d, *J* = 18.8 Hz, 1H), 2.32 (dt, *J* = 14.7, 2.3 Hz, 1H), 2.19 (s, 6H), 2.17 – 2.06 (m, 3H), 2.06 – 1.96 (m, 2H), 1.89 (td, *J* = 12.8, 4.0 Hz, 1H), 1.80 (dd, *J* = 13.0, 4.1 Hz, 1H), 1.26 (d, *J* = 6.6 Hz, 3H), 1.19 (d, *J* = 6.4 Hz, 3H), 1.07 (ddt, *J* = 9.4, 7.4, 4.6 Hz, 24H), 0.96 (s, 9H), 0.14 (d, *J* = 2.9 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.4, 187.2, 186.8, 161.1, 156.6, 156.0, 135.8, 135.6, 134.3, 134.2, 121.0, 119.9, 118.5, 111.5, 111.4, 101.5, 99.9, 74.1, 73.8, 70.6, 69.6, 68.8, 67.3, 66.7, 61.8, 56.8, 43.5, 35.7, 34.1, 33.4, 26.0, 18.1, 17.8, 17.8, 17.7, 17.6, 17.6, 17.5, 17.5, 17.4, 17.4, 14.4, 14.3, 13.2, 12.7. HRMS: $[M + H]^+$ calculated for $C_{53}H_{84}NO_{15}Si_3$ 1058.51488; found 1058.51488.

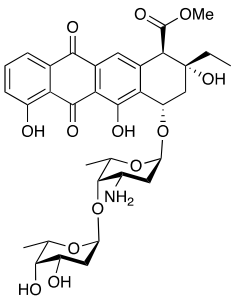
To a solution of the above compound (38 mg, 35.9 μmol) in pyridine (3.6 mL) in a PTFE tube, was added HF.pyr complex (70 wt% HF, 282 μL) at 0°C. Over the course of 4.5 hours, 3 additional such portions of HF.pyr complex were added. Then, solid $NaHCO_3$ was added to quench and the mixture was stirred until cessation of effervescence. It was then filtered off and concentrated *in vacuo*. Column chromatography on neutral silica (DCM – 10:90 MeOH:DCM) gave the title compound as a red solid (20.3 mg, 28.9 μmol, 81%). ^{1}H NMR (500 MHz, Chloroform-*d* + MeOD) δ 8.02 (d, *J* = 7.6 Hz, 1H), 7.81 (t, *J* = 8.0 Hz, 1H), 7.42 (t, *J* = 7.3 Hz, 1H), 5.55 (d, *J* = 4.0 Hz, 1H), 5.28 (s, 1H), 5.05 (d, *J* = 3.9 Hz, 1H), 4.76 (d, *J* = 5.6 Hz, 2H), 4.41 (q, *J* = 6.6 Hz, 1H), 4.14 – 4.03 (m, 4H), 3.97 (q, *J* = 6.6 Hz, 1H), 3.83 (d, *J* = 6.5 Hz, 1H), 3.24 (dd, *J* = 18.9, 5.9 Hz, 1H), 3.02 (dd, *J* = 19.2, 6.3 Hz, 1H), 2.39 – 2.08 (m, 8H), 2.07 – 1.80 (m, 4H), 1.29 (d, *J* = 6.7 Hz, 3H), 1.21 (d, *J* = 6.6 Hz, 3H).^{13}C NMR (126 MHz, $CDCl_3$ + MeOD) δ 213.6, 187.2, 186.8, 161.1, 155.9, 155.3, 135.9, 135.4, 133.8, 133.5, 120.8, 119.8, 118.6, 111.6, 111.4, 100.9, 99.2, 73.6, 71.0, 69.2, 68.6, 66.6, 65.4, 65.2, 61.7, 56.6, 43.0, 35.5, 33.8, 32.3, 28.7, 17.9, 16.6. HRMS: $[M + H]^+$ calculated for $C_{35}H_{44}NO_{14}$ 702.27619; found 702.2769.

7-[2-Deoxy-3,4-tetraisopropyldisiloxyl-α-L-fucopyranosyl-(1→4)-3-amino-2,3-dideoxy-α-L-fucopyranoside]-aklavinone (71)



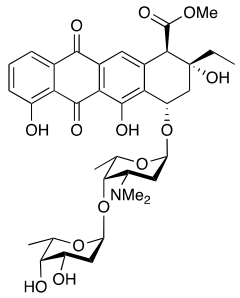
Prepared according to General Procedure C from donor **68** (623 mg, 0.806 mmol) and aklavinone **43** (665 mg, 1.61 mmol, 2.00 eq) at -20°C to give after column chromatography (10:90 EtOAc:pentane and then 2:98 – 10:90 acetone:toluene) of the residue an inseparable mixture of the disaccharide anthracycline and acceptor, which was continued to the next step. A solution of the above mixture and *N,N*-dimethylbarbituric acid (562 mg, 3.60 mmol, 2.2 eq) in DCM (81 mL) was degassed for 5 minutes. Then, $Pd(PPh_3)_4$ (23 mg, 0.040 mmol, 0.025 eq) was added and the mixture was allowed to stir for 30 minutes. It was then directly subjected to column chromatography (pentane, then 0:100 – 25:75 acetone:toluene) to give the title compound as a yellow solid (636 mg, 0.700 mmol, 86% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.76 (d, *J* = 7.5 Hz, 1H), 7.70 – 7.58 (m, 2H), 7.25 (d, *J* = 8.4 Hz, 1H), 5.47 (d, *J* = 2.8 Hz, 1H), 5.25 (dd, *J* = 4.1, 1.8 Hz, 1H), 4.97 (d, *J* = 3.6 Hz, 1H), 4.42 (ddd, *J* = 12.0, 4.7, 2.5 Hz, 1H), 4.19 – 4.05 (m, 3H), 4.00 (d, *J* = 2.6 Hz, 1H), 3.70 (s, 3H), 3.51 (d, *J* = 2.5 Hz, 1H), 3.24 (qt, *J* = 9.3, 6.6, 5.6 Hz, 1H), 2.52 (dd, *J* = 15.0, 4.3 Hz, 1H), 2.36 – 2.28 (m, 1H), 2.17 – 2.08 (m, 1H), 2.01 (dd, *J* = 12.3, 4.6 Hz, 1H), 1.86 – 1.68 (m, 3H), 1.49 (dd, *J* = 14.1, 7.0 Hz, 1H), 1.30 (d, *J* = 6.4 Hz, 3H), 1.23 (d, *J* = 6.5 Hz, 3H), 1.17 – 0.85 (m, 31H).^{13}C NMR (101 MHz, $CDCl_3$) δ 192.6, 181.2, 171.4, 162.5, 162.1, 142.7, 137.4, 133.4, 132.9, 131.2, 124.8, 120.9, 120.2, 115.7, 114.6, 101.7, 101.1, 81.7, 73.3, 71.6, 70.9, 70.2, 68.1, 67.8, 57.1, 52.6, 46.8, 33.9, 33.4, 32.2, 17.7, 17.7, 17.6, 17.5, 17.5, 17.4, 17.3, 17.3, 14.3, 14.1, 13.1, 12.6, 6.8. HRMS: $[M + H]^+$ calculated for $C_{46}H_{68}NO_{14}Si_2$ 914.4178; found 914.4173.

7-[2-Deoxy-α-L-fucopyranosyl-(1→4)-3-amino-2,3-dideoxy-α-L-fucopyranoside]-aklavinone (6)



To a solution of **71** (91 mg, 0.10 mmol) in pyridine (10 mL) in a PTFE tube, was added HF.pyr complex (70 wt% HF, 393 µL) at 0°C. Over the course of 4.5 hours, 3 additional such portions of HF.pyr complex were added. Then, solid $NaHCO_3$ was added to quench and the mixture was stirred until cessation of effervescence. It was then filtered off and partitioned between DCM and H_2O. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography on neutral silica (DCM – 20:80 MeOH:DCM) followed by size-exclusion chromatography (Sephadex LH-20, eluent DCM:MeOH, 1:1) gave the title compound as a yellow solid (27.5 mg, 40.9 µmol, 41%). ^{1}H NMR (400 MHz, Chloroform-*d* + MeOD) δ 7.79 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.74 – 7.57 (m, 2H), 7.32 – 7.23 (m, 1H), 5.47 (t, *J* = 2.5 Hz, 1H), 5.27 – 5.20 (m, 1H), 4.97 (d, *J* = 3.5 Hz, 1H), 4.20 – 4.01 (m, 4H), 3.70 (s, 3H), 3.64 (d, *J* = 3.0 Hz, 2H), 3.61 – 3.52 (m, 2H), 3.11 (dd, *J* = 10.6, 6.7 Hz, 1H), 2.53 (dd, *J* = 15.0, 4.4 Hz, 1H), 2.27 (d, *J* = 15.0 Hz, 1H), 1.97 (ddd, *J* = 22.5, 12.3, 4.2 Hz, 2H), 1.86 – 1.64 (m, 3H), 1.50 (dt, *J* = 14.6, 7.4 Hz, 1H), 1.28 (d, *J* = 6.4 Hz, 3H), 1.23 (d, *J* = 6.5 Hz, 3H), 1.07 (q, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.6, 181.4, 171.4, 162.5, 162.0, 142.6, 137.5, 133.5, 132.9, 131.1, 124.9, 121.0, 120.3, 115.8, 114.7, 101.3, 100.8, 81.1, 71.6, 70.9, 70.8, 68.0, 67.4, 65.4, 57.0, 52.6, 46.7, 34.1, 33.2, 32.7, 32.2, 17.3, 16.9, 6.7. HRMS: $[M + H]^+$ calculated for $C_{34}H_{42}NO_{13}$ 672.2656; found 672.2645.

7-[2-Deoxy-α-L-fucopyranosyl-(1→4)-3-dimethylamino-2,3-dideoxy-α-L-fucopyranoside]-aklavinone (8)



To a solution of **6** (26.2 mg, 37.4 µmol) in EtOH (3.7 mL) and 37% aq. CH_2O (200 µL, 60 eq) was added $NaBH(OAc)_3$ (85 mg, 0.374 mmol, 10 eq). The mixture was stirred for 2.5 hours before being poured into sat. aq. $NaHCO_3$. This was extracted with DCM, dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography on neutral silica (3:97 – 10:90 MeOH:DCM) gave the title compound as a yellow solid (8.8 mg, 12.6 µmol, 34%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 12.69 (s, 1H), 12.04 (s, 1H), 7.83 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.78 – 7.60 (m, 2H), 7.31 (dd, *J* = 8.4, 1.2 Hz, 1H), 5.51 (d, *J* = 3.7 Hz, 1H), 5.27 (dd, *J* = 4.3, 1.9 Hz, 1H), 5.01 (s, 1H), 4.53 (dd, *J* = 14.2, 7.7 Hz, 1H), 4.17 – 4.05 (m, 2H), 4.00 (q, *J* = 6.6 Hz, 1H), 3.74 (d, *J* = 8.5 Hz, 1H), 3.63 (d, *J* = 3.1 Hz, 1H), 2.52 (dd, *J* = 15.0, 4.3 Hz, 1H), 2.29 (dd, *J* = 16.9, 9.2 Hz, 1H), 2.25 – 2.11 (m, 6H), 2.07 (dt, *J* = 10.9, 5.4 Hz, 1H), 1.87 – 1.79 (m, 1H), 1.75 (dq, *J* = 14.6, 7.7, 7.3 Hz, 1H), 1.51 (dq, *J* = 14.3, 7.2 Hz, 1H), 1.28 (d, *J* = 6.5 Hz, 3H), 1.20 (d, *J* = 6.5 Hz, 3H), 1.09 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 192.9, 181.5, 162.7, 162.3, 142.8, 137.5, 133.6, 133.1, 124.9, 121.1, 120.3, 116.0, 114.8, 101.7, 99.2, 71.8, 71.7, 70.8, 68.5, 66.3, 66.0, 61.7, 57.3, 52.7, 43.4, 33.9, 33.2, 32.3, 18.0, 16.8, 6.8. HRMS: $[M + H]^+$ calculated for $C_{36}H_{46}NO_{13}$ 700.2969; found 700.2966.

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Chapter 4

Changing the 3'-substitution pattern on doxorubicin

Introduction

Since the discovery of doxorubicin in 1969,[1] it has become one of the most used anti-cancer drugs, with an annual market of over $800 million.[2] In spite of its efficacy against (amongst others) leukemia and non-Hodgkin's lymphoma,[3] the use of this drug is limited by its cardiotoxic side effect.[4] In the search for more potent anthracyclines with fewer side-effects, several thousands of analogs of daunorubicin and doxorubicin have been isolated from natural source, produced by mutant enzymes or prepared by organic synthesis.[5,6] Disappointingly, only a handful of these made it to a clinical setting (see Chapter 1) as these were not significantly more potent or less cardiotoxic enough, and doxorubicin itself remains the most used anti-cancer anthracycline. Chapter 1 discussed the recently uncovered mechanism of action of anthracyclines, namely histone eviction.[7] It was shown that doxorubicin is both able to induce both DNA DSBs and histone eviction, whereas the much less cardiotoxic aclarubicin only possesses the latter ability, prompting the hypothesis that histone eviction may be the most important mechanism of action by which anthracyclines cause cancer cell death.

In order to understand what structural elements in doxorubicin and aclarubicin result in this differential activity profile, Chapter 3 presented a coherent set of hybrid structures between these two drugs in which the aglycone, amine/dimethylamine and sugar chain were varied. This Chapter focuses more deeply on further varying the 3'-amine by synthesizing 11 doxorubicin analogs that differ in this position. These include neutral 3'-analogs (lacking the basic amine), 3'-methyl analogs that introduce steric bulk onto the daunosamine ring, singly *N*-methylated and doubly *N*-ethylated doxorubicin and finally *N*-heterocyclic doxorubicins.

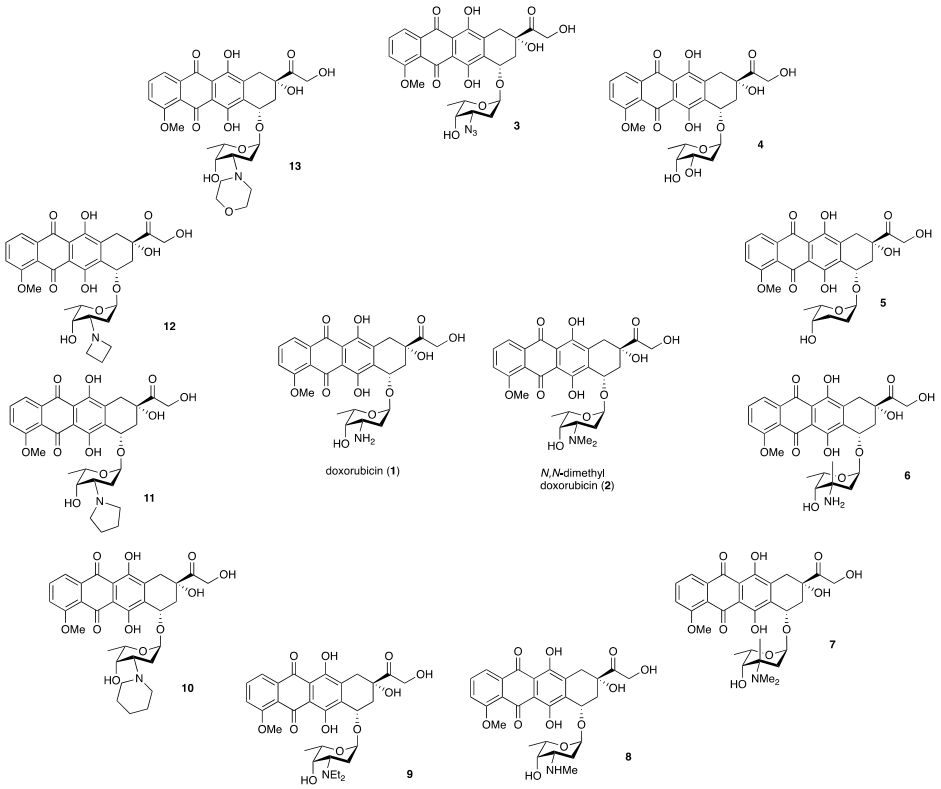


Figure 1. Chemical structures of the doxorubicin derivatives **3**-**13** subject of this Chapter, differing in substitution pattern on the 3-position of the sugar moiety.

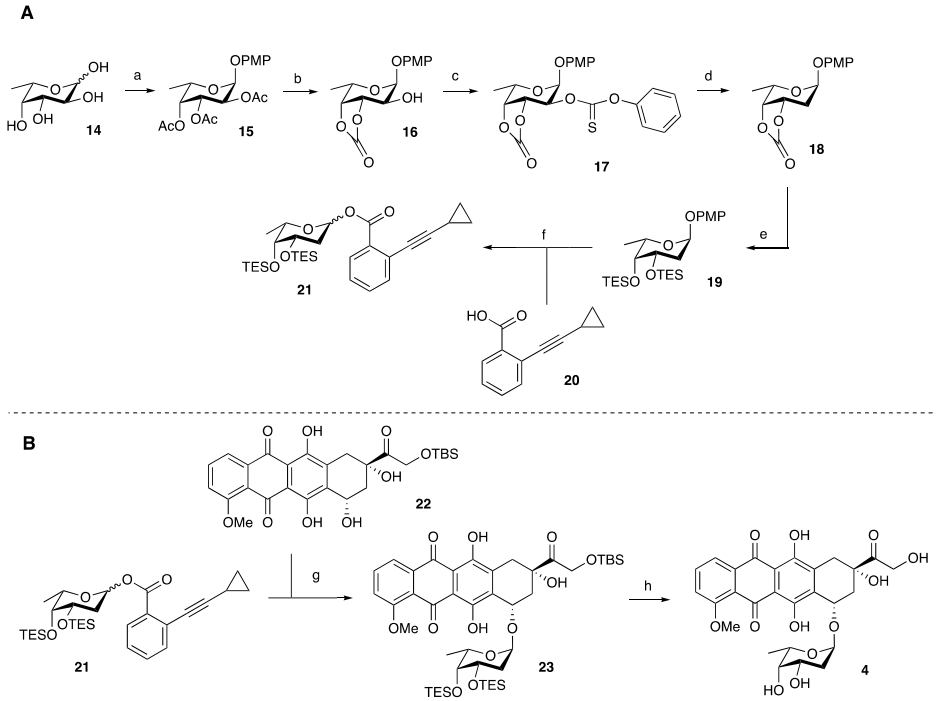
Depicted in the middle of the circle in Figure 1 are doxorubicin (**1**) and *N,N*-dimethyldoxorubicin (**2**) (see also Chapter 2). Compounds **3**, **4** and **5** represent non-basic analogs of doxorubicin, all lacking the amine that would be protonated at physiological pH. The absence of a basic amine may have implications for the intracellular processing of the compound,[8] for example by altering interactions with negatively charged DNA backbones[9] and by abolishing P-glycoprotein recognition.[10] In known azidodoxorubicin (**3**),[10,11] the amine is masked as an azide. Second, in 3'-desamino-3'-hydroxydoxorubicin (**4**), the amine function in doxorubicin is replaced with a hydroxyl instead, keeping the hydrogen bonding ability of the 3-position. This compound was earlier prepared by means of modified Koenigs-Knorr glycosylation in the group of Varela in 1984 in their search for an improved doxorubicin analogue.[12] *In vivo* evaluation in the P388 lymphocytic leukemia system in mice showed decreased cytotoxicity when compared to doxorubicin (**1**), with later evaluation by Capranico *et al.*[13] showing that hydroxyrubicin (**4**) is no less potent than doxorubicin with respect to the induction of DNA breaks. A difference in their respective histone evicting abilities

might be able to explain the difference in cytotoxicity instead. Third, 3'-desaminodoxorubicin (**5**) was designed, lacking any substituent on the 3-position of the sugar moiety.

Vancosaminyl doxorubicinone (**6**) and its *N,N*-dimethylated analog (**7**) were envisaged to introduce steric bulk on the ring, with the introduction of a 3'-Me substituent. Its sugar moiety, L-vancosamine, can be prepared *de novo,*[14–16] from sugars/amino acids,[17–19] or it can be cleaved off of its parent drug vancomycin.[20,21] This Chapter shows the application of the latter strategy in the assembly of these two doxorubicin-vancomycin hybrids. *N*-methyldoxorubicin (**8**) fills the chemical space in between doxorubicin (**1**) and its *N,N*-dimethyldoxorubicin (**2**). Elaborating further on this theme, *N,N*-diethyldoxorubicin (**9**) was designed, a compound previously prepared by Tong *et al*.,[22] bearing a sterically less accessible amine compared to **2**. *N*-cyclic doxorubicins (**10**-**13**) were designed in the same vein, offering cyclic structures as a means of sterically constraining the tertiary amine. Compound **10-12** contain a piperidino, pyrrolidino and azetidino moiety, respectively. Morpholino-doxorubicin (also known as KRN8602(MX2)) (**13**) has already been evaluated in phase II trials but has not yet been probed within the context of histone eviction.[23] This compound introduces an oxygen in the ring versus **10**, giving rise to intramolecular hydrogen bonding with the amine, lowering its basicity.[24]

Although many of these compounds have been previously reported in the literature, their biological evaluation was often incomplete (e.g. not tested for histone evicting property). The availability of these compounds will aid in establishing an in-depth structure-activity relationship to explain the different biological activities of doxorubicin and provide insight how to manipulate these.

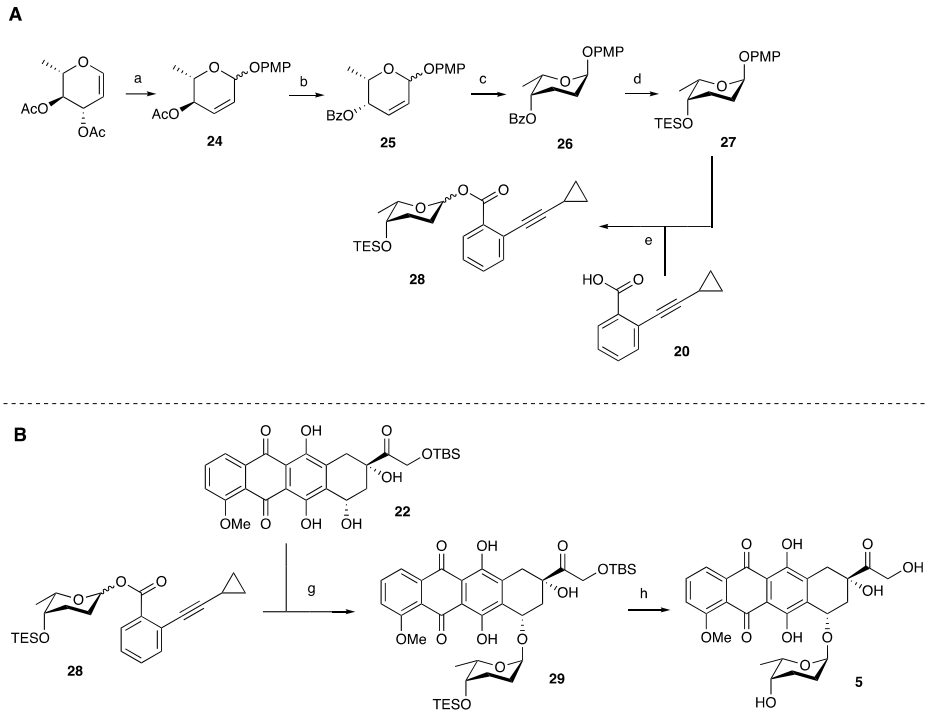
Results and discussion



Scheme 1. Synthesis of 3'-desamino-3'-hydroxydoxorubicin (**4**). *Reagents and conditions:* (a) *i.* Ac_2O, pyr.; *ii. p*-methoxyphenol, $BF_3{\cdot}OEt_2$, DCM, 0 °C to RT, 76% over 2 steps; (b) *i.* NaOMe, MeOH; *ii.* carbonyldiimidazole, DMF, 85 °C, quant. over 2 steps; (c) *O*-phenyl thionochloroformate, pyr., DCM, 92%; (d) Bu_3SnH, AIBN, toluene, 80 °C, 85%; (e) *i.* NaOMe, MeOH; *ii.* triethylsilyl triflate, pyr., DMF, 64% over 2 steps; (f) *i.* Ag(II)(hydrogen dipicolinate)$_2$, NaOAc, ACN, H_2O, 0 °C; *ii.* EDCI·HCl, DIPEA, DMAP, DCM, 61% over 2 steps (1:9 α:β); (g) PPh_3AuNTf_2, DCM, 63% (α-only); (h) HF·pyridine, THF/pyr., 78%.

Azidodoxorubicin (**3**) was prepared in Chapter 2 by means of copper-catalysed diazotransfer on doxorubicin (**1**).[11] Key step the synthesis of hydroxydoxorubicin (**4**) in Scheme 1 is the glycosylation of anomeric *ortho*-alkynylbenzoate **21** to doxorubicinone-acceptor **22** by means of catalytic gold(I) activation, according to the method developed by Yu's group and discussed in more detail in Chapter 2 and 3.[25] Peracetylation of L-fucose **14** was followed by treatment with $BF_3{\cdot}OEt_2$ in the presence of *p*-methoxyphenol to give α-fucoside **15** in good yield according to literature procedure.[26] Subjection to global deacetylation was followed by installation of a 3,4-carbonate function as a temporary protecting group using carbonyldiimidazole to furnish **16** quantitatively. Then, the 2-hydroxyl was transformed to its corresponding *O*-phenyl-thiono-carbonate **17**.[27] Treatment of **17** with excess tributyltin hydride and a catalytic amount of AIBN cleanly afforded 2-deoxy fucoside **18**. The carbonate was then subjected to Zemplén conditions and the resulting diol disilylated to yield **19**. This was converted into the

corresponding *ortho*-alkynylbenzoate donor **21** by means of silver(II)-mediated oxidation of the anomeric *p*-methoxyphenolate, followed by Steglich esterification of the resultant hemiacetal to carboxylic acid **20**. Treatment of a mixture of this donor **21** and 14-*O*-TBS-doxorubicinone **22** with catalytic PPh_3AuNTf_2 gave the desired anthraquinone glycoside **23** with good α-selectivity. Desilylation (using HF·pyridine) afforded hydroxyrubicin **4**, whose spectral data were in agreement with those reported in the literature.[12]

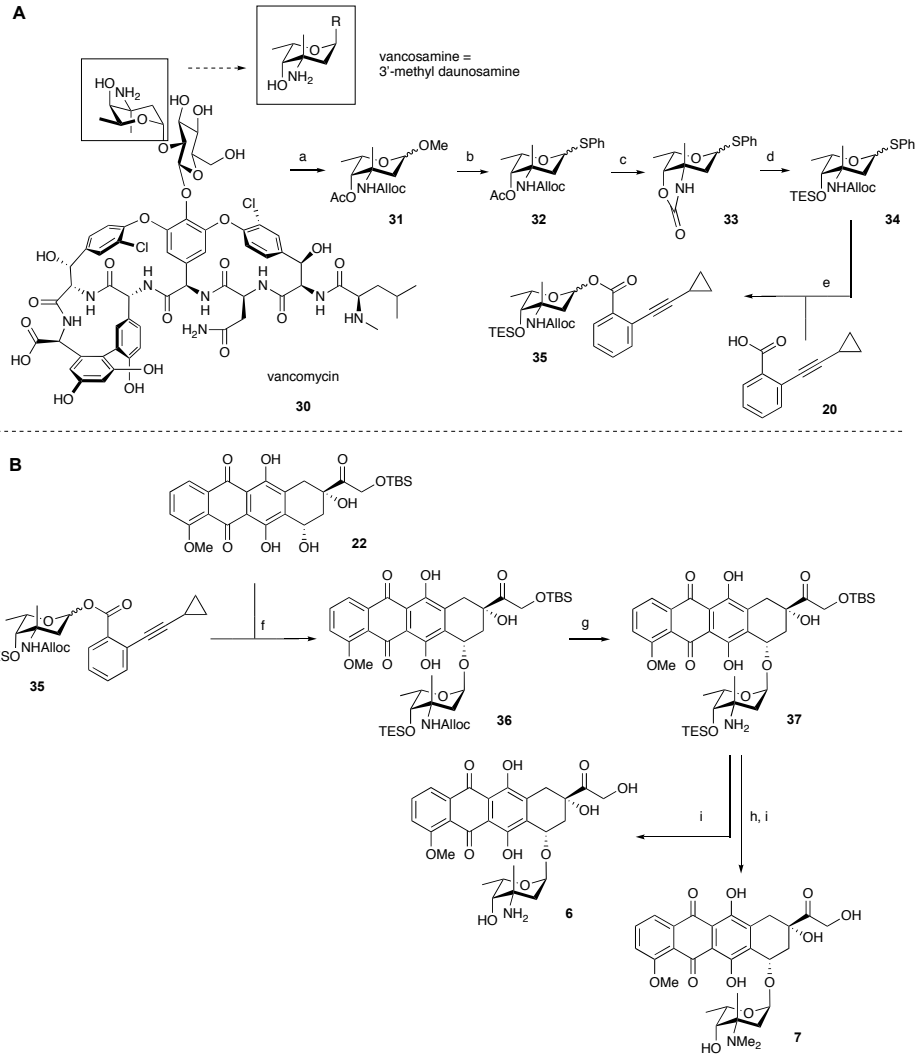


Scheme 2. Synthesis of 3'-desaminodoxorubicin (**5**). *Reagents and conditions:* (a) *p*-methoxyphenol, $BF_3{\cdot}OEt_2$, toluene, -10 °C, 41%, (12.5:1 α:β); (b) *i.* NaOMe, MeOH; *ii.* benzoic acid, PPh_3, diethylazodicarboxylate, THF, 0 °C to RT, 80% over 2 steps; (c) Rh/Al_2O_3, H_2, toluene, EtOAc, 0 °C, quant.; (d) *i.* NaOMe, MeOH; *ii.* triethylsilyl triflate, pyr., DMF, 73% over 2 steps; (e) *i.* Ag(II)(hydrogen dipicolinate)$_2$, NaOAc, ACN, H_2O, 0 °C; *ii.* EDCI·HCl, DIPEA, DMAP, DCM, 61% over 2 steps (1:9 α:β); (g) PPh_3AuNTf_2, DCM, 39% (α-only); (h) HF·pyridine, THF/pyr., 93%.

The synthesis of 3'-desaminodoxorubicin (**5**) commenced with L-rhamnal (Chapter 2), as depicted in Scheme 2A. Treatment hereof with *p*-methoxyphenol in toluene at -10 °C in the presence of 5 mol% $BF_3{\cdot}OEt_2$ afforded enopyranoside **24**, according to literature procedure.[28] The Lewis acid was used in low amount to suppress the amount of rearrangement of the phenolic O-glycoside to the aryl-C-glycoside.[29] Under these conditions, the reported[28] yield of 91% could not be reproduced: instead only 41% of

the product could be isolated from a complex mixture. The 4-acetate in **24** was then subjected to deacetylation under Zemplén conditions and ensuing Mitsunobu inversion of the resulting allylic alcohol to give 4-benzoate **25**. Rhodium-catalysed hydrogenation of the double bond yielded rhodinoside **26**. Debenzoylation and silylation yielded **27**, which was subjected to oxidative cleavage of the anomeric *p*-methoxyphenolate, followed by esterification to **20** to give *ortho*-alkynylbenzoate **28** in good yield. Treatment of this donor with PPh_3AuNTf_2 in the presence of acceptor **22** delivered **29** α-selectively (Scheme 2B), but in only 39% yield, likely due to instability of the reactive intermediates of this highly deoxygenated donor. A final HF·pyridine-mediated desilylation afforded desaminodoxorubicin (**5**).

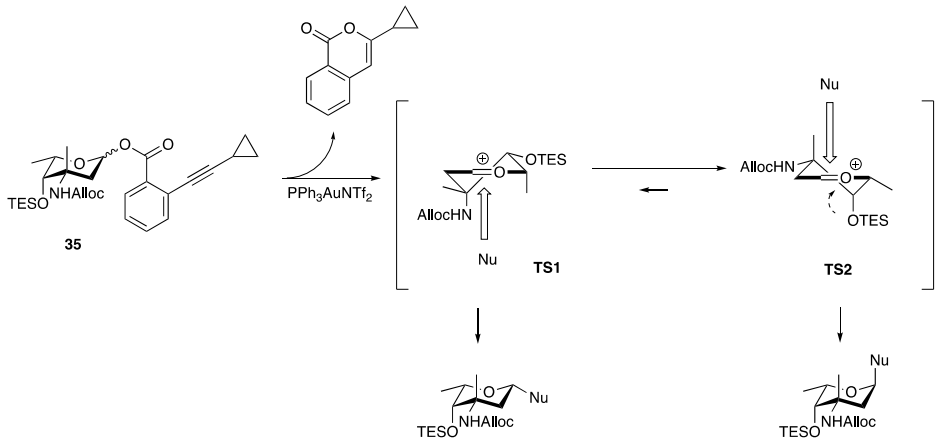
The synthesis of (*N,N*-dimethyl)-vancosaminyl doxorubicinones **6** and **7** is depicted in Scheme 3. Vancomycin (**30**), commercially available and relatively inexpensive ($350/50g at Carbosynth[30]) has been shown to be suitable for obtaining vancosamine-related glycosyl donors by the groups of Kahne and Bennett.[20,21] Combining lessons learned from their procedures, both amines found in vancomycin **30** were protected as their Alloc-carbamates using Alloc-succinimide, after which acidic methanolysis liberated the vancosamine synthon from its aglycone (Scheme 3A). After acetylation of its 4-hydroxyl function, protected vancosamine **31** was obtained in 57% over the three steps. Installation of a thiophenyl group on the anomeric position gave **32** as an anomeric mixture. 4-Deacylation under Zemplén conditions was accompanied by intramolecular attack onto the neighboring carbamate to give 3,4-carbamate **33**, with concomitant release of allyl alcohol. Hydrolysis of the carbamate in refluxing aqueous sodium hydroxide gave the free amine, and re-installation of the *N*-Alloc-group and 4-silylation to afford fully protected **34** in 90% yield over the three steps. Treatment of thioglycoside **34** with silver nitrate and lutidine afforded the corresponding hemiacetal.[31,32] Presumably, a silver-dilutidinium complex[33] is formed which is able to effect hydrolysis of the thioether. Ensuing Steglich esterification of this hemiacetal yielded *ortho*-alkynylbenzoate **35**. Activation of alkynylbenzoate **35** (Scheme 3B) by means of PPh_3AuNTf_2 in the presence of doxorubicinone-acceptor **22** afforded **36** as a 6:1 α:β mixture with respect to the newly formed anomeric center, for which a mechanistic rationale is shown in Scheme 4. In line with the stereoselective additions reported in Chapter 2 and 3, it is proposed that oxocarbenium ion-like intermediates are at the basis of the observed stereoselectivity. The oxocarbenium ion in TS1 is stabilized by the axial allyloxycarbamate. However, the most favorable trajectory for the incoming nucleophile is blocked by this same group. The alternative TS2 features an oxocarbenium ion, that places the C4-*O*-TBS group in an optimal orientation to provide electronic stabilization of the electron depleted anomeric center.



Scheme 3. Synthesis of (*N,N*-dimethyl)-vancosaminyl doxorubicinones **6** and **7**. *Reagents and conditions:* (a) *i.* Alloc-OSu, $NaHCO_3$, THF, H_2O; *ii.* HCl, MeOH; *iii.* Ac_2O, DMAP, pyr., 57% over 3 steps; (b) PhSH, $BF_3{\cdot}OEt_2$, DCM, 0 °C to RT, 83%; (c) NaOMe, MeOH, 88%; (d) *i.* aq. NaOH, 110°C; *ii.* Alloc-OSu, $NaHCO_3$, THF, H_2O (1:1, v/v); *iii.* triethylsilyl triflate, pyr., DCM, 90% over 3 steps; (e) *i.* $AgNO_3$, 2,6-lutidine, THF, H_2O; *ii.* EDCI·HCl, DIPEA, DMAP, DCM, 45% over 2 steps (1:10 α:β); (f) PPh_3AuNTf_2, DCM, 68% (6:1 α:β); (g) $Pd(PPh_3)_4$, NDMBA, DCM, 77%; (h) aq. CH_2O, $NaBH(OAc)_3$, EtOH; then Alloc-OSu, DCM, 52% over 2 steps; (i) HF·pyridine, pyr., 89% for **6**, 88% for **7**.

It also positions the C5-methyl group in a sterically favorable *pseudo*-equatorial position. Attack on this half chair oxocarbenium ion preferentially occurs on the top (*i.e.* α)-face to lead to the product through a chair-like transition state. Additionally,

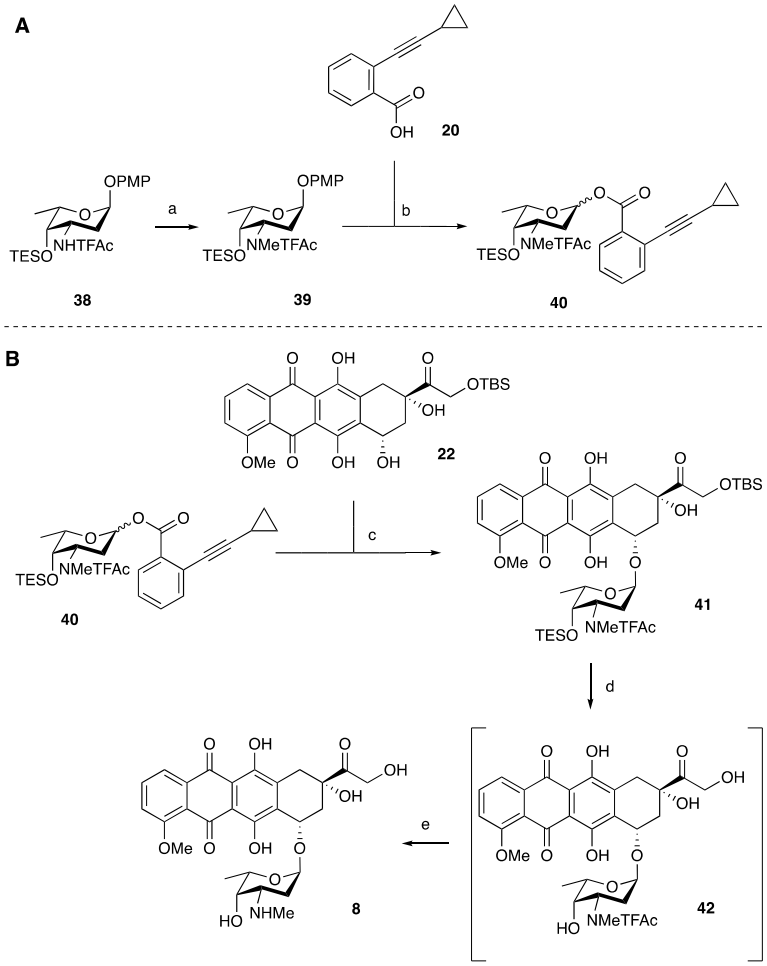
neighboring-group participation of the 3-Alloc group would also yield the α-product, which cannot be excluded at this stage.[34]



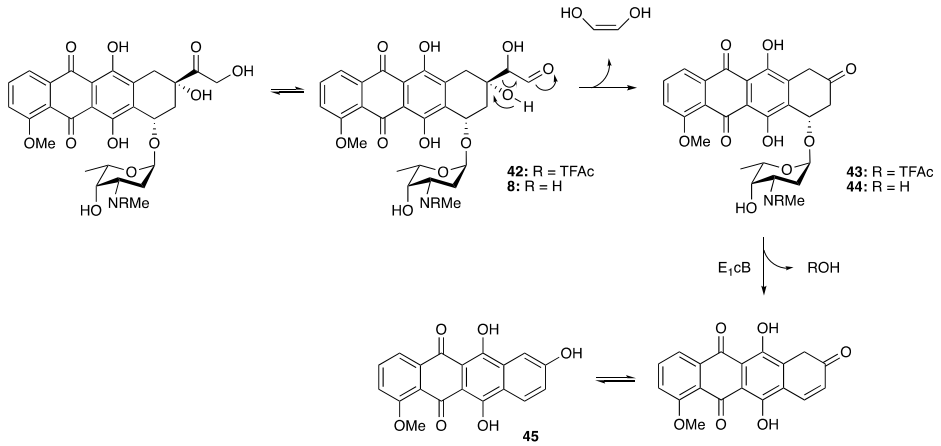
Scheme 4. Mechanistic rationale for the observed stereoselectivity of the glycosylation of donor **19** to acceptor **22**.

The desired, pure α-glycoside **36** could be isolated from the mixture by silica gel column chromatography. Alloc-removal with $Pd(PPh_3)_4$/NDMBA cleanly afforded the free amine in **37**. Desilylation thereof gave 3'-Me-doxorubicin (**6**) in good yield. Reductive amination (CH_2O, $NaBH(OAc)_3$) afforded a mixture of the starting amine and its mono- and dimethylated products, which could not be separated at this stage. Treatment of the mixture with a large excess of Alloc-OSu capped the undesired (*N*-methyl)-amine to facilitate isolation of the pure dimethylated amine in modest yield over these two steps, whose sugar moiety is known as brasiliose.[35] A final desilylation gave 3'-Me-dimethyldoxorubicin **7**.

The synthesis of *N*-monomethyldoxorubicin **8** is depicted in Scheme 5. Acetamide **38** (Chapter 2) was alkylated using iodomethane in acetone, using potassium carbonate as the base. The anomeric *p*-methoxyphenolate in **39** was then converted into its anomeric *ortho*-alkynylbenzoate **40** as described earlier in this Chapter. A mixture of this donor **40** and 14-*O*-TBS-doxorubicinone **22** was treated with PPh_3AuNTf_2 to give **41** α-selectively. After global desilylation hereof using triethylamine trihydrofluoride, the removal of the trifluoroacetamide (excess NaOMe, MeOH[36]) proceeded alongside extensive degradation towards the 9-ketone and fully aromatized **47**. A putative mechanism for this process is shown in Scheme 6.



Scheme 5. Synthesis of *N*-monomethyldoxorubicin **8**. *Reagents and conditions:* (a) MeI, K_2CO_3, acetone, 50 °C, quant.; (b) *i.* Ag(II)(hydrogen dipicolinate)$_2$, NaOAc, MeCN, H_2O, 0 °C; *ii.* EDCI·HCl, DIPEA, DMAP, DCM, 70% over 2 steps (1:5 α:β); (c) PPh_3AuNTf_2, DCM, 71%; (d) triethylamine·3HF, THF/pyr.; (e) NaOMe, MeOH, 23% over 2 steps.

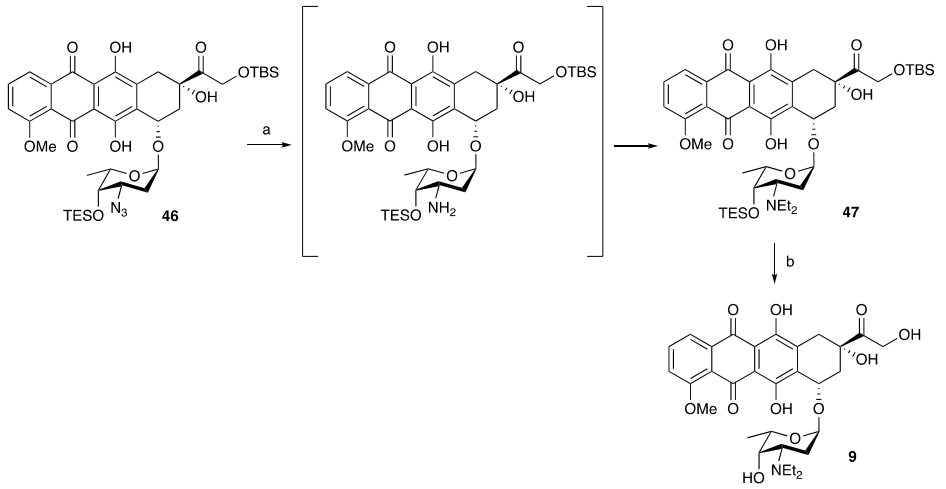


Scheme 6. Degradation of **8** and **42** *via* the bis-(hydroxy)ketone moiety.

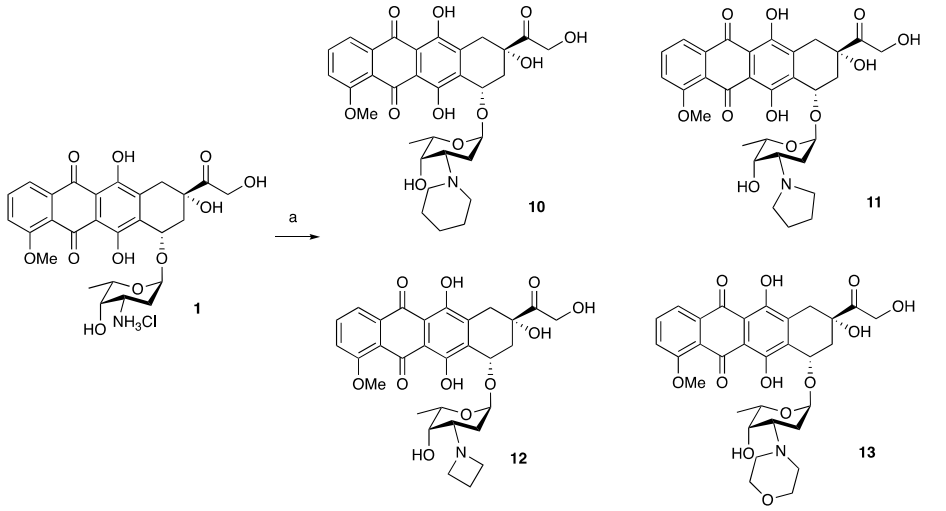
Tautomerisation of the exocyclic hydroxyketone can give rise to base-induced release of ethene-1,2-diol in a *retro*-aldol fashion to give **43**/**44**. This delivers a good substrate for E_1cB elimination, releasing the glycan and giving an enone that tautomerizes to give the phenol in **45**. This type of degradation was also observed by Tong *et al*.[37] during regular silica gel column chromatography of *N,N*-dialkyl doxorubicins and daunorubicins, and by Penco *et al.*[38] upon acid treatment of doxorubicin derivatives. Nevertheless, *N*-monomethylated **8** was obtained in 23% yield over the two steps after extensive purification. Glycosylation of the *N*-Me-Alloc alkynylbenzoate to acceptor **22** proceeded in poor yield (22%) and degraded during attempted removal of the Alloc group.

For the synthesis of *N,N*-diethyldoxorubicin **9**, protected doxorubicin **46** (Chapter 2) was subjected to Staudinger reduction conditions, followed by reductive amination using ethanolic acetaldehyde to afford the dialkylated product **47** in modest yield over both steps. A similar drop in yield upon reductive diethylation when compared to dimethylation was observed by Tong *et al.*,[22] who also prepared **9**. Final desilylation gave *N,N*-diethyldoxorubicin (**9**) near quantitatively.

N-cyclic doxorubicins **10-13** could be prepared in a single step by means of dialkylation of the amine in doxorubicin (**1**) to form the heterocycle, according to a previously reported procedure.[39] Treatment of doxorubicin with diiodopentane, diiodobutane, diiodopropane or bis(2-iodo)ethyl ether in the presence of triethylamine afforded **10**-**13** respectively, in modest yields but good final purity.



Scheme 7. Synthesis of *N,N*-diethyldoxorubicin **9**. *Reagents and conditions:* (a) *i.* polymer-bound PPh_3, THF, H_2O, 50 °C; *ii.* ethanolic acetaldehyde, $NaBH(OAc)_3$, EtOH, 30% over 2 steps; (b) HF·pyr., pyr., 98%.



Scheme 8. Synthesis of *N*-cyclic doxorubicins **10**-**13**. *Reagents and conditions:* (a) corresponding diiodoalkane, Et_3N, DMF, 25% for **10**, 53% for **11**, 34% for **12**, 60% for **13**.

Conclusions

Despite doxorubicin (**1**) having been used in a clinical setting for several decades, its structure-activity relationship is still not fully understood. Its use is still plagued by cumulative cardiotoxicity, severely limiting treatment. Histone eviction having been recently uncovered to be a previously unknown mode of action of anthracyclines brings renewed interest and incentive to make doxorubicin analogs. The synthesis and biological evaluation of coherent sets of analogs should aid in understanding the structure-activity relationship of this oft-used anti-cancer drug. To this end, this Chapter describes the synthesis of 11 derivatives of doxorubicin (**1**), differing in substitution pattern on the 3'-position of the sugar. Hydroxyrubicin (**4**) and desaminodoxorubicin (**5**), *N*-monomethyl- and *N,N*-diethyldoxorubicin (**8**) and (**9**) were prepared through the appropriate multiply deoxygenated *ortho*-alkynylbenzoate glycosyl donors from either L-rhamnose or L-fucose, followed by gold(I)-catalysed glycosylation.

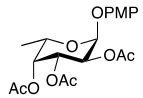
As Chapter 2 and 3 demonstrated the hydrolysis of natural glycosides doxorubicin and aclarubicin to obtain their respective aglycons, in this Chapter the methanolysis of vancomycin facilitated the isolation of its sugar moiety vancosamine which was used for the synthesis of **6** and **7**. This strategy of cleaving rare sugars off of natural products and appending them onto anthracycline aglycones can be expanded to other (bacterial) secondary metabolites to yield additional doxorubicin analogs.

N-cyclic doxorubicins **10**-**13** and azidodoxorubicin **3** could be prepared in a single reaction from the parent compound doxorubicin (**1**). The focused library of doxorubicin analogs **4**-**13** together with the ones described in Chapters 3 and 5 can now be evaluated for their ability to induce DNA breaks, cardiotoxic effects and chromatin damage as well as the regio-selectivity thereof within the genome, to aid in establishing a proper structure-activity relationship to explain the biological activities of anthracyclines.

Experimental procedures and characterization data

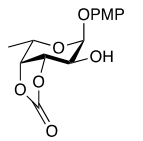
All reagents were of commercial grade and used as received. Traces of water from reagents were removed by co-evaporation with toluene in reactions that required anhydrous conditions. All moisture/oxygen sensitive reactions were performed under an argon atmosphere. DCM used in the glycosylation reactions was dried with flamed 4Å molecular sieves before being used. Reactions were monitored by TLC analysis with detection by UV (254 nm) and where applicable by spraying with 20% sulfuric acid in EtOH or with a solution of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4\cdot 2H_2O$ (10 g/L) in 10% sulfuric acid (aq.) followed by charring at ~150 °C. Flash column chromatography was performed on silica gel (40-63µm). ^{1}H and ^{13}C spectra were recorded on a Bruker AV 400 and Bruker AV 500 in $CDCl_3$, CD_3OD, pyridine-*d5* or D_2O. Chemical shifts (δ) are given in ppm relative to tetramethylsilane (TMS) as internal standard (^{1}H NMR in $CDCl_3$) or the residual signal of the deuterated solvent. Coupling constants (J) are given in Hz. All ^{13}C spectra are proton decoupled. Column chromatography was carried out using silica gel (0.040-0.063 mm). Size-exclusion chromatography was carried out using Sephadex LH-20, using DCM:MeOH (1:1, v/v) as the eluent. Neutral silica was prepared by stirring regular silica gel in aqueous ammonia, followed by filtration, washing with water and heating at 150°C overnight. High-resolution mass spectrometry (HRMS) analysis was performed with a LTQ Orbitrap mass spectrometer (Thermo Finnigan), equipped with an electronspray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10 mL/min, capillary temperature 250 °C) with resolution R = 60000 at m/z 400 (mass range m/z = 150 – 2000) and dioctyl phthalate (m/z = 391.28428) as a "lock mass", or with a Synapt G2-Si (Waters), equipped with an electronspray ion source in positive mode (ESI-TOF), injection via NanoEquity system (Waters), with LeuEnk (m/z = 556.2771) as "lock mass". Eluents used: MeCN:H_2O (1:1 v/v) supplemented with 0.1% formic acid. The high-resolution mass spectrometers were calibrated prior to measurements with a calibration mixture (Thermo Finnigan).

_p_-Methoxyphenyl-2,3,4-O-acetyl-α-L-fucopyranoside (15)[26]



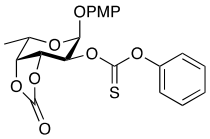
Commercially available L-fucose (6.53 g, 39.8 mmol) was suspended in pyridine (155 mL) and acetic anhydride (77 mL), to which DMAP (690 mg, 5.65 mmol, 0.14 eq) was added. After stirring overnight, the mixture was concentrated *in vacuo*. It was then partitioned between EtOAc and 1M HCl, and the organic layer was successively washed with sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo* to give the crude peracetylated fucose. This was then together with *p*-methoxyphenol (7.41 g, 59.7 mmol, 1.5 eq) coevaporated from toluene and dissolved in DCM (320 mL). Then at 0°C, $BF_3\cdot OEt_2$ (8.42 mL, 79.6 mmol, 2 eq) was added and the mixture was allowed to warm up to RT overnight. It was then poured into sat. aq. $NaHCO_3$, and the organic layer was washed with 1M NaOH, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (9:1:1 pentane:EtOAc:DCM) gave the title compound as a colourless syrup (12.5g, 31.6 mmol, 79% over 3 steps). Spectral data was in accordance with that of literary precedence.[26]

_p_-Methoxyphenyl-3,4-O-carbonate-α-L-fucopyranoside (16)



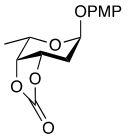
To a solution of **15** (10.38 g, 26.2 mmol) in MeOH (180 mL) was added NaOMe until pH>10 and the mixture was stirred for 3.5 hours. It was then neutralized by addition of AcOH and concentrated *in vacuo* to yield the corresponding triol. This crude triol was then dissolved in DMF (100 mL) and added dropwise to a solution of carbonyl diimidazole (4.25 g, 26.2 mmol, 1 eq) in DMF (130 mL) by syringe pump over 1 hour at 85 °C. Thereafter, 1M HCl (200 mL) was added and the mixture was stirred for a further 15 minutes at the same temperature. It was then diluted with EtOAc and washed with H_2O thrice and sat. aq. $NaHCO_3$. Drying over $MgSO_4$ and concentration *in vacuo* gave the title compound as a white solid (7.76 g, 26.2 mmol, quant. over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.09 – 6.91 (m, 2H), 6.91 – 6.79 (m, 2H), 5.40 (d, *J* = 4.0 Hz, 1H), 4.97 (dd, *J* = 7.5, 5.7 Hz, 1H), 4.68 (dd, *J* = 7.6, 2.1 Hz, 1H), 4.37 (qd, *J* = 6.6, 2.1 Hz, 1H), 4.18 (dt, *J* = 6.1, 3.0 Hz, 1H), 3.77 (s, 3H), 3.49 (d, *J* = 4.0 Hz, 1H), 1.32 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6, 154.3, 150.1, 118.2, 114.8, 95.9, 77.0, 76.0, 66.6, 63.8, 55.7, 15.6. HRMS: $(M + Na)^+$ calculated for $C_{14}H_{16}O_7Na$ 319.0794; found 319.0788.

***p*-Methoxyphenyl-3,4-O-carbonate-2-*O*-(phenoxy)thiocarbonyl-α-L-fucopyranoside (17)**



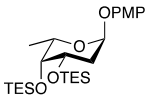
To a solution of **16** (6.70 g, 22.6 mmol) in DCM/pyr (220 mL, 1:1 v/v), after which *O*-phenyl chlorothionoformate (4.84 mL, 1.55 eq) was added at 0°C. After stirring overnight, MeOH (6 mL) was added to quench and the mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc and H_2O, then the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (5-20% EtOAc in pentane) gave the title compound as an orange foam (9.00g, 20.8 mmol, 92%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.47 – 7.36 (m, 2H), 7.36 – 7.29 (m, 1H), 7.16 – 7.08 (m, 2H), 7.09 – 6.95 (m, 2H), 6.91 – 6.80 (m, 2H), 5.85 (d, *J* = 3.7 Hz, 1H), 5.63 (dd, *J* = 7.6, 3.7 Hz, 1H), 5.24 (dd, *J* = 7.6, 6.9 Hz, 1H), 4.79 (dd, *J* = 6.9, 2.6 Hz, 1H), 4.33 (qd, *J* = 6.7, 2.6 Hz, 1H), 3.79 (s, 3H), 1.44 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.1, 155.8, 153.5, 153.4, 150.2, 129.8, 127.1, 121.8, 117.7, 114.9, 93.8, 78.0, 77.7, 74.5, 63.2, 55.8, 15.8. HRMS: $(M + Na)^+$ calculated for $C_{21}H_{20}O_8SNa$ 455.0777; found 455.0778.

***p*-Methoxyphenyl-2-deoxy-3,4-*O*-carbonate-α-L-fucopyranoside (18)**



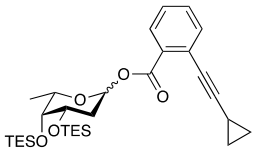
A solution of **17** (2.12 g, 4.90 mmol), tributyltin hydride (3.95 mL, 14.7 mmol, 3 eq) and AIBN (0.2M in toluene, 0.98 mmol, 0.2 eq) in toluene (160 mL) was heated at 100°C for 10 minutes. It was then allowed to cool to room temperature, washed with 1M NaOH, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (20:80 – 40:60 Et_2O:pentane) gave the title compound as a colourless oil (1.16 g, 4.14 mmol, 85%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.06 – 6.89 (m, 2H), 6.89 – 6.74 (m, 2H), 5.53 (t, *J* = 6.3 Hz, 1H), 5.08 (dt, *J* = 8.3, 3.6 Hz, 1H), 4.60 (dd, *J* = 8.4, 1.8 Hz, 1H), 4.18 (qd, *J* = 6.6, 1.8 Hz, 1H), 3.77 (s, 3H), 2.62 (ddd, *J* = 15.7, 5.9, 4.0 Hz, 1H), 2.11 (ddd, *J* = 15.8, 6.8, 3.4 Hz, 1H), 1.32 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.3, 154.4, 150.7, 118.3, 114.7, 95.0, 76.0, 72.5, 64.1, 55.8, 29.1, 15.5. HRMS: $(M + Na)^+$ calculated for $C_{14}H_{16}O_6Na$ 303.0845; found 303.0847.

***p*-Methoxyphenyl-2-deoxy-3,4-*O*-triethylsilyl -α-L-fucopyranoside (19)**



To a solution of **18** (420 mg, 1.5 mmol) in MeOH (3.8 mL) was added NaOMe (16 mg, 0.30 mmol, 0.2 eq) and the mixture was allowed to stir overnight. It was quenched by addition of dry ice and concentrated *in vacuo* to yield the corresponding diol. This was then dissolved in DMF (7.6 mL), to which pyridine (0.70 mL, 8.7 mmol, 5.8 eq) and triethylsilyl triflate (1.2 mL, 5.1 mmol, 3.4 eq) were added at 0°C. The resulting mixture was allowed to stir overnight, after which another portion of both reagents was added at 0°C, and the mixture was allowed to stir overnight once again. It was then poured into EtOAc, washed with H_2O 5x, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (100:1 pentane:Et_3N – 90:10:1 pentane:Et_2O:Et_3N) gave the title compound as a clear oil (460 mg, 0.95 mmol, 64% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.06 – 6.90 (m, 2H), 6.90 – 6.72 (m, 2H), 5.50 (d, *J* = 3.2 Hz, 1H), 4.18 (ddd, *J* = 11.7, 4.5, 2.5 Hz, 1H), 3.92 (q, *J* = 6.5 Hz, 1H), 3.77 (s, 3H), 3.64 (d, *J* = 2.5 Hz, 1H), 2.20 (td, *J* = 12.3, 3.6 Hz, 1H), 1.78 (ddt, *J* = 12.7, 4.6, 1.3 Hz, 1H), 1.15 (d, *J* = 6.5 Hz, 3H), 0.99 (dt, *J* = 8.9, 8.0 Hz, 18H), 0.78 – 0.44 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8, 151.7, 118.0, 114.9, 97.8, 73.9, 68.7, 67.9, 56.1, 33.6, 17.8, 7.5, 7.3, 5.7, 5.3. HRMS: $(M + Na)^+$ calculated for $C_{25}H_{46}O_5Si_2Na$ 505.2782; found 505.2777.

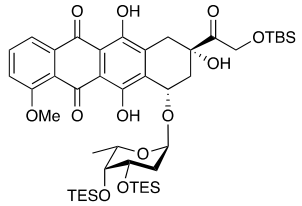
***o*-Cyclopropylethynylbenzoyl-2-deoxy-3,4-*O*-triethylsilyl-L-fucopyranoside (21)**



To a solution of **19** (450 mg, 0.93 mmol) in MeCN:H_2O (50 mL, 1:1 v/v) were added NaOAc (808 mg, 9.3 mmol, 10 eq) and then $Ag(DPAH)_2 \cdot H_2O$ (1.76 g, 3.72 mmol, 4 eq) portionwise over 30 minutes at 0°C. The mixture was stirred for 3.5 hours; after which it was poured into sat. aq. $NaHCO_3$. This was then extracted with DCM thrice, dried over $MgSO_4$ and concentrated *in vacuo* to give the crude lactol. To a solution of this in DCM were added DIPEA (0.75 mL, 4.2 mmol, 4.5 eq), DMAP (119 mg, 0.93 mmol, 1 eq), EDCI·HCl (581 mg, 2.93 mmol, 3.2 eq) and freshly saponified cyclopropylethynylbenzoic acid **20** (559 mg, 2.79 mmol, 3 eq). After stirring overnight, the mixture was diluted with DCM and washed with sat. aq. $NaHCO_3$ and brine. Drying over $MgSO_4$, concentration *in vacuo* and column chromatography of the residue (2:98 – 4:96 EtOAc:pentane) followed by size-exclusion chromatography (Sephadex LH-20, 1:1 DCM:MeOH v/v) gave the

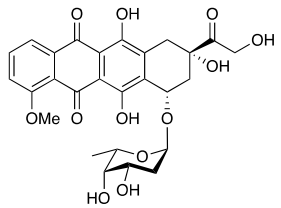
title compound as a white solid (312 mg, 0.57 mmol, 1:9 α:β, 62% over 2 steps). Spectral data for the β-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.99 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.54 – 7.34 (m, 2H), 7.29 (qd, *J* = 7.3, 1.4 Hz, 1H), 5.90 (dd, *J* = 10.2, 2.3 Hz, 1H), 3.77 (ddd, *J* = 11.9, 4.3, 2.6 Hz, 1H), 3.65 – 3.55 (m, 2H), 2.20 (td, *J* = 11.8, 10.1 Hz, 1H), 1.82 (dddd, *J* = 11.6, 4.3, 2.3, 1.0 Hz, 1H), 1.55 – 1.47 (m, 1H), 1.28 (d, *J* = 6.3 Hz, 3H), 0.98 (tt, *J* = 7.5, 3.8 Hz, 18H), 0.92 – 0.85 (m, 4H), 0.76 – 0.54 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.7, 134.2, 132.0, 131.0, 131.0, 127.0, 125.1, 99.8, 93.2, 74.7, 72.7, 72.5, 70.8, 33.8, 17.3, 9.0, 7.2, 6.9, 5.3, 4.9, 0.8. HRMS: (M + Na)$^+$ calculated for $C_{30}H_{48}O_5Si_2Na$ 567.2938; found 567.2946.

7-[2-Deoxy-3,4-*O*-triethylsilyl-α-L-fucopyranoside]-14-*O*-*tert*-butyldimethylsilyl-doxorubicinone (23)



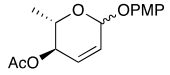
To a solution of glycosyl donor **21** (207 mg, 0.38 mmol) and the glycosyl acceptor **22** (301 mg, 0.57 mmol, 1.5 eq) in DCM (7.6 mL), activated molecular sieves (4Å) were added. The mixture was stirred for 30 minutes at room temperature andthen a freshly prepared 0.1M DCM solution of PPh_3AuNTf_2 (prepared by stirring 1:1 PPh_3AuCl and $AgNTf_2$ in DCM for 30 minutes) (0.38 mL, 0.1 eq) in DCM was added dropwise. After 15 minutes, the mixture was filtered and concentrated *in vacuo*. Column chromatography (20:80 Et_2O:pentane and then 1:99 – 2:98 acetone:toluene) of the residue gave the title compound as a red solid (211 mg, 0.24 mmol, 63%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.83 (s, 1H), 13.12 (s, 1H), 7.93 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.73 (t, *J* = 8.1 Hz, 1H), 7.37 (dd, *J* = 8.6, 1.1 Hz, 1H), 5.50 (d, *J* = 3.8 Hz, 1H), 5.23 (dd, *J* = 4.0, 2.2 Hz, 1H), 5.01 – 4.83 (m, 2H), 4.79 (s, 1H), 4.08 (s, 3H), 3.91 (q, *J* = 6.4 Hz, 1H), 3.77 (ddd, *J* = 12.0, 4.6, 2.4 Hz, 1H), 3.69 – 3.56 (m, 1H), 3.11 (dd, *J* = 19.0, 1.9 Hz, 1H), 2.86 (d, *J* = 18.8 Hz, 1H), 2.32 (dt, *J* = 14.8, 2.1 Hz, 1H), 2.15 – 2.05 (m, 2H), 1.58 (dd, *J* = 12.9, 4.5 Hz, 1H), 1.26 (d, *J* = 6.3 Hz, 4H), 1.04 – 0.92 (m, 18H), 0.87 (t, *J* = 7.9 Hz, 9H), 0.67 (qd, *J* = 8.3, 7.9, 3.7 Hz, 6H), 0.53 (qd, *J* = 8.3, 7.9, 1.9 Hz, 6H), 0.15 (d, *J* = 2.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.5, 186.8, 186.5, 161.0, 156.4, 155.7, 135.6, 135.4, 134.1, 120.8, 119.7, 118.4, 111.2, 101.6, 73.4, 69.0, 68.9, 67.5, 66.7, 56.7, 35.4, 34.0, 32.9, 26.0, 18.7, 17.5, 7.1, 6.8, 5.3, 4.8, -5.2. HRMS: (M + Na)$^+$ calculated for $C_{45}H_{70}O_{12}Si_3Na$ 909.4073; found 909.4107.

7-[2-Deoxy-α-L-fucopyranoside]-doxorubicinone (4)



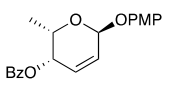
23 (105 mg, 0.118 mmol) was dissolved in THF:pyr (12.3 mL, 2:1 v/v), to which HF·pyr complex (743 µL) was added at 0°C. After stirring for 3 hours, the same amount of HF·pyr complex was added and the mixture was stirred a further 1.5 hours. It was then poured into sat. aq. $NaHCO_3$, extracted with DCM twice, dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography on neutral silica (33:66 – 50:50 acetone:toluene) gave a solid, which was triturated with $CHCl_3$ and filtered. Evaporation of the filtrate gave the title compound as a red solid (50 mg, 92 µmol, 78%). Analytical data were in agreement with literature precedence.[12] ^{1}H NMR (400 MHz, Pyridine-d_5) δ 8.08 (d, *J* = 7.6 Hz, 1H), 7.82 (t, *J* = 8.1 Hz, 1H), 7.51 (d, *J* = 8.5 Hz, 1H), 5.85 (d, *J* = 3.8 Hz, 1H), 5.50 – 5.37 (m, 3H), 4.68 (q, *J* = 6.4 Hz, 1H), 4.52 (ddd, *J* = 12.1, 4.9, 2.9 Hz, 1H), 4.06 (s, 4H), 3.53 (q, *J* = 18.4 Hz, 2H), 2.92 – 2.83 (m, 1H), 2.65 (td, *J* = 12.5, 4.0 Hz, 1H), 2.54 (dd, *J* = 14.4, 5.1 Hz, 1H), 2.38 (dd, *J* = 12.7, 4.9 Hz, 1H), 1.58 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, Pyr) δ 215.5, 187.8, 162.1, 136.9, 135.2, 124.7, 121.7, 120.2, 112.5, 112.1, 103.2, 77.3, 72.5, 71.4, 68.8, 67.0, 66.1, 57.4, 38.0, 34.5, 34.2, 18.2. HRMS: (M + H)$^+$ calculated for $C_{27}H_{29}O_{12}$ 545.1659; found 545.2017.

***p*-Methoxyphenyl-4-*O*-acetyl-2,3,6-trideoxy-L-*erythro*-hexopyranoside (24)**[28,40]



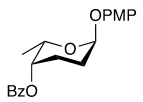
3,4-di-*O*-acetyl-L-rhamnal (Chapter 2) (3.96 g, 18.5 mmol) and *p*-methoxyphenol (2.48 g, 20.0 mmol, 1.08 eq) were jointly coevaporated from toluene, after which they were dissolved in toluene (150 mL). To this solution at -10 °C was added $BF_3{\cdot}OEt_2$ (0.11 mL, 0.93 mmol, 0.05 eq) and the mixture was stirred at this temperature for 2 h. It was then poured into sat. aq. $NaHCO_3$ and extracted with DCM. The resulting organic layer was washed with 1M NaOH and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (5:95 Et_2O:pentane) gave the title compound as a white solid (2.13 g, 7.65 mmol, 41%, 12.5:1 α:β). Spectral data was in accordance with that of literary precedence.[28,40]

***p*-Methoxyphenyl-4-*O*-benzoyl-2,3,6-trideoxy-L-*threo*-hexopyranoside (25)**



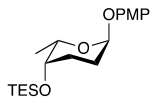
To a solution of **24** (2.13 g, 7.65 mmol, 12.5:1 α:β) in MeOH (77 mL) was added NaOMe (83 mg, 1.54 mmol, 0.2 eq) and the mixture was stirred for 1.5 hours. It was then quenched by addition of dry ice and concentrated *in vacuo*. The residue was partitioned between EtOAc and H_2O, after which the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The resulting allylic alcohol was then dissolved in THF (17 mL), together with benzoic acid (1.96 g, 16.1 mmol, 2.1 eq) and triphenylphosphine (4.21 g, 16.1 mmol, 2.1 eq). To this, diethyl azodicarboxylate (4.6 mL, 14.9 mmol, 1.95 eq) was added dropwise at 0°C. After stirring overnight, the reaction mixture was concentrated *in vacuo*. Then, Et_2O was added to the residue and this was filtered off. The filtrate was washed with sat. aq. $NaHCO_3$ twice, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (5:95 Et_2O:pentane) gave the title compound as an orange oil (2.07 g, 6.08 mmol, 80% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.11 – 8.08 (m, 2H), 7.58 (ddt, *J* = 7.8, 6.9, 1.3 Hz, 1H), 7.50 – 7.41 (m, 2H), 7.10 – 7.06 (m, 2H), 6.93 – 6.83 (m, 2H), 6.33 (ddd, *J* = 9.9, 5.5, 1.1 Hz, 1H), 6.21 (ddd, *J* = 9.9, 3.2, 0.6 Hz, 1H), 5.71 – 5.64 (m, 1H), 5.23 (ddd, *J* = 5.5, 2.5, 0.6 Hz, 1H), 4.51 (qd, *J* = 6.6, 2.5 Hz, 1H), 3.79 (s, 3H), 1.31 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 155.1, 151.5, 133.4, 129.9, 128.6, 126.8, 118.4, 114.7, 94.1, 65.9, 65.5, 55.8, 16.3. HRMS: $(M + Na)^+$ calculated for $C_{20}H_{20}O_5Na$ 363.1208; found 363.1214.

***p*-Methoxyphenol-4-O-benzoyl-2,3-dideoxy-α-L-fucopyranoside (26)**



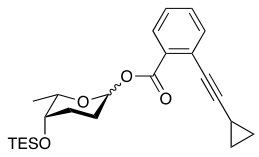
To a solution of **25** (2.07 g, 6.08 mmol) in toluene:EtOAc (9:1 v/v, 125 mL) was added rhodium on alumina (5% rhodium, 250 mg) at 0°C. The reaction was then placed under hydrogen atmosphere and stirred overnight. It was then filtered off over Celite and concentrated *in vacuo* to give the title compound as a light-yellow solid (2.08 g, 6.08 mmol, quant.). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.15 – 8.12 (m, 2H), 7.59 (ddt, *J* = 8.7, 7.0, 1.3 Hz, 1H), 7.54 – 7.40 (m, 2H), 7.10 – 6.99 (m, 2H), 6.88 – 6.79 (m, 2H), 5.57 (d, *J* = 2.6 Hz, 1H), 5.12 (s, 1H), 4.25 (qd, *J* = 6.6, 1.5 Hz, 1H), 3.78 (s, 3H), 2.37 (tdd, *J* = 14.0, 4.6, 2.8 Hz, 1H), 2.21 – 2.10 (m, 1H), 2.10 – 1.96 (m, 1H), 1.83 (ddt, *J* = 13.5, 4.0, 1.8 Hz, 1H), 1.16 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 154.7, 151.2, 133.2, 130.4, 129.8, 128.6, 117.7, 114.7, 96.4, 70.0, 66.2, 55.8, 24.6, 23.1, 17.4. HRMS: $(M + Na)^+$ calculated for $C_{20}H_{22}O_5Na$ 365.1365; found 365.1362.

***p*-Methoxyphenol-2,3-dideoxy-1-thio-α-L-fucopyranoside (27)**



A solution of **26** (2.08 g, 6.08 mmol) in dioxane (40 mL), MeOH (40 mL) and 1M NaOH (20 mL) was stirred at 60 °C for 2.5 hours, after which it was concentrated *in vacuo*. The residue was partitioned between EtOAc and sat. aq. NH_4Cl, after which the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The crude alcohol was then redissolved in DMF (10 mL), after which pyridine (1.47 mL, 18.2 mmol, 3 eq) and triethylsilyl triflate (2.47 mL, 10.9 mmol, 1.8 eq) were added at 0°C and allowed to stir overnight. The reaction mixture was then partitioned between EtOAc and sat. aq. $NaHCO_3$, after which the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (2:98:1 – 5:95:1 Et_2O:pentane:Et_3N) gave the title compound as a light yellow oil (1.57 g, 4.45 mmol, 73% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.08 – 6.91 (m, 2H), 6.89 – 6.70 (m, 2H), 5.46 (t, *J* = 2.0 Hz, 1H), 4.05 – 3.89 (m, 1H), 3.77 (s, 3H), 3.67 – 3.62 (m, 1H), 2.23 – 2.15 (m, 2H), 1.75 – 1.63 (m, 2H), 1.10 (d, *J* = 6.5 Hz, 3H), 0.99 (t, *J* = 7.9 Hz, 9H), 0.73 – 0.55 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4, 151.5, 117.6, 114.6, 96.4, 67.8, 55.8, 26.5, 23.9, 17.6, 7.1, 5.0. HRMS: $(M + Na)^+$ calculated for $C_{19}H_{32}O_4SiNa$ 375.1968; found 375.197.

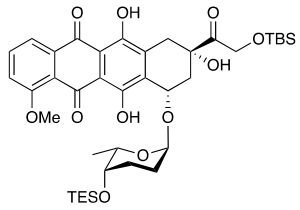
***o*-Cyclopropylethynylbenzoyl-2,3-dideoxy-4-*O*-triethylsilyl-L-fucopyranoside (28)**



To a solution of **27** (386 mg, 0.93 mmol) in MeCN:H_2O (50 mL, 1:1 v/v) were added NaOAc (808 mg, 9.3 mmol, 10 eq) and then $Ag(DPAH)_2 \cdot H_2O$ (1.76 g, 3.72 mmol, 4 eq) at 0°C. The mixture was stirred for 30 minutes; after which it was poured into sat. aq. $NaHCO_3$. This was then extracted with DCM thrice, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (10:90 – 50:50 Et_2O:pentane) gave the lactol. To a solution of this in DCM were added DIPEA (0.75 mL, 4.2 mmol, 4.5 eq), DMAP (119 mg, 0.93 mmol, 1 eq), EDCI·HCl (581 mg, 2.93 mmol, 3.2 eq) and freshly saponified cyclopropylethynylbenzoic acid **20** (559 mg, 2.79 mmol, 3 eq). After stirring overnight, the mixture was diluted with

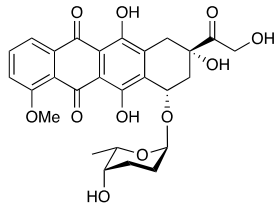
DCM and washed with sat. aq. $NaHCO_3$ and brine. Drying over $MgSO_4$, concentration *in vacuo* and column chromatography of the residue (5:95 EtOAc:pentane) followed by size-exclusion chromatography (Sephadex LH-20, 1:1 DCM:MeOH v/v) gave the title compound as a white solid (236 mg, 0.803 mmol, 82% over 2 steps, 1:4 α:β). Spectral data for the β-anomer: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.02 – 7.97 (m, 1H), 7.47 (td, *J* = 7.6, 1.3 Hz, 1H), 7.44 – 7.35 (m, 1H), 7.35 – 7.27 (m, 1H), 5.96 (dd, *J* = 9.0, 2.4 Hz, 1H), 3.79 (qd, *J* = 6.5, 1.9 Hz, 1H), 3.63 (p, *J* = 2.2 Hz, 1H), 2.14 – 2.05 (m, 1H), 1.98 (dq, *J* = 13.4, 5.3, 4.6 Hz, 1H), 1.82 – 1.72 (m, 2H), 1.51 (ddd, *J* = 8.2, 5.2, 2.8 Hz, 1H), 1.26 (d, *J* = 6.5 Hz, 3H), 0.99 (td, *J* = 7.9, 3.7 Hz, 9H), 0.93 – 0.82 (m, 4H), 0.64 (q, *J* = 7.9 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.8, 134.3, 131.8, 131.4, 130.9, 127.0, 125.1, 99.7, 95.2, 75.5, 67.0, 29.8, 25.1, 17.4, 9.0, 7.0, 5.0, 0.8. HRMS: (M + Na)$^+$ calculated for $C_{24}H_{34}O_4SiNa$ 437.2124; found 437.2126.

7-[2,3-Dideoxy-4-*O*-triethylsilyl-α-L-fucopyranoside]-14-*O*-*tert*-butyldimethylsilyl-doxorubicinone (29)



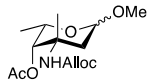
To a solution of glycosyl donor **28** (61 mg, 0.183 mmol) and the glycosyl acceptor **22** (109 mg, 0.27 mmol, 1.5 eq) in DCM (3.7 mL), activated molecular sieves (4Å) were added. The mixture was stirred for 30 minutes at room temperature andthen a freshly prepared 0.1M DCM solution of PPh_3AuNTf_2 (prepared by stirring 1:1 PPh_3AuCl and $AgNTf_2$ in DCM for 30 minutes) (0.19 mL, 0.1 eq) in DCM was added dropwise. After 15 minutes, the mixture was filtered and concentrated *in vacuo*. Column chromatography (20:80 Et_2O:pentane and then 1:99 acetone:toluene) of the residue gave the title compound as a red solid (43 mg, 0.057 mmol, 39%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.89 (s, 1H), 13.24 (s, 1H), 8.00 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.76 (t, *J* = 8.1 Hz, 1H), 7.38 (dd, *J* = 8.6, 1.1 Hz, 1H), 5.43 (d, *J* = 3.5 Hz, 1H), 5.29 (dd, *J* = 4.1, 2.2 Hz, 1H), 5.03 – 4.81 (m, 3H), 4.08 (s, 3H), 3.98 (tt, *J* = 6.5, 3.6 Hz, 1H), 3.67 (s, 1H), 3.19 (dd, *J* = 18.9, 1.9 Hz, 1H), 2.99 (d, *J* = 18.9 Hz, 1H), 2.38 (dt, *J* = 14.8, 2.2 Hz, 1H), 2.22 – 1.96 (m, 2H), 1.75 (tt, *J* = 13.4, 3.6 Hz, 1H), 1.61 (dd, *J* = 13.7, 3.9 Hz, 1H), 1.56 – 1.40 (m, 1H), 1.20 (d, *J* = 6.4 Hz, 3H), 0.97 (d, *J* = 7.2 Hz, 18H), 0.63 (q, *J* = 7.9 Hz, 6H), 0.14 (d, *J* = 2.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.6, 187.1, 186.7, 161.1, 156.5, 156.0, 135.7, 135.6, 134.5, 134.2, 121.0, 119.9, 118.5, 111.5, 111.3, 101.0, 69.3, 68.4, 67.6, 66.8, 56.8, 35.6, 34.1, 26.4, 26.0, 23.5, 18.7, 17.6, 7.1, 5.0, -5.3. HRMS: (M + Na)$^+$ calculated for $C_{39}H_{56}O_{11}Si_2Na$ 779.3259; found 779.3276.

3'-Desaminodoxorubicin (5)



29 (21 mg, 28 µmol) was dissolved in THF/pyr (3 mL, 2:1 v/v), to which HF·pyr complex (356 µL) was added at 0°C. After stirring for 1 hour, it was poured into sat. aq. $NaHCO_3$, extracted with DCM twice, dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography on neutral silica (20:80 acetone:toluene) gave the title compound as a red solid (14 mg, 26 µmol, 93%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.95 (s, 1H), 13.23 (s, 1H), 8.02 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.88 – 7.71 (m, 1H), 7.40 (dd, *J* = 8.5, 1.2 Hz, 1H), 5.45 (d, *J* = 3.8 Hz, 1H), 5.34 (dd, *J* = 3.9, 2.2 Hz, 1H), 4.97 (s, 1H), 4.77 (s, 2H), 4.19 – 4.02 (m, 4H), 3.67 (s, 1H), 3.32 – 3.17 (m, 1H), 3.10 – 2.93 (m, 2H), 2.38 (dt, *J* = 14.6, 2.2 Hz, 1H), 2.16 (dd, *J* = 14.6, 4.0 Hz, 1H), 2.01 (tdd, *J* = 11.4, 8.5, 5.0 Hz, 1H), 1.78 (dq, *J* = 10.3, 3.4 Hz, 2H), 1.55 (dd, *J* = 14.3, 3.7 Hz, 1H), 1.26 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.0, 187.2, 186.8, 161.2, 156.4, 155.8, 135.9, 135.6, 134.1, 133.8, 121.0, 119.9, 118.6, 111.6, 111.5, 100.8, 69.2, 67.7, 67.1, 65.6, 56.8, 35.6, 34.2, 25.7, 23.2, 17.3. HRMS: (M + Na)$^+$ calculated for $C_{27}H_{28}O_{11}Na$ 551.1529; found 551.1533.

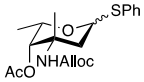
Methyl 3-*N*-allyloxycarbonyl-4-*O*-acetyl-L-vancosamine (31)[20,21]



A suspension of vancomycin hydrochloride **30** (22.0 g, 14.8 mmol) and $NaHCO_3$ (4.0 g, 47.4 mmol, 3.2 eq) in dioxane/H_2O (400 mL, 1:1 v/v) was stirred for 30 minutes. To the resulting pink solution was added allyloxycarbonyl succinimide (12.0 g, 59.2 mol, 4 eq) in dioxane (10 mL) and the resulting mixture was stirred for 3 hours, after which it was then poured into acetone (3 L) and stirred vigorously for 1h. It was then filtered, the residue was collected and the filter was thoroughly rinsed with MeOH. This wash and the residue were jointly concentrated *in vacuo*, coevaporated with toluene and

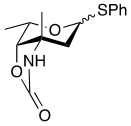
dried under high vacuum overnight to yield crude bis-*N*-Alloc-vancomycin (23.7 g, max. 14.8 mmol) as a light pink solid. This was redissolved in MeOH (250 mL), to which 4M methanolic HCl (prepared by adding acetyl chloride to MeOH, 40 mL) was added. After 3 hours, $NaHCO_3$ (15 g) was portionwise added to the resulting light-yellow suspension until neutral pH. The tan suspension was then filtered and the filter was thoroughly rinsed with MeOH. This wash and the residue were concentrated *in vacuo* until precipitation, after which acetone (1L) was added. The resulting suspension was stirred for 10 minutes and filtered over a paper funnel, and the filtrate was concentrated *in vacuo* to yield a brown sludge. This was dissolved in a minimal amount of MeOH, after which it was loaded onto a silica gel column equilibrated to 80:20 pentane:EtOAc. This was eluted with 80:20 – 100:0 pentane:EtOAc, and all fractions containing the desired product were filtered and the filtrate was concentrated *in vacuo*. The residue was absorbed onto Celite from MeOH, after which column chromatography (30:70 – 50:50 EtOAc:pentane) yielded the crude methyl 3-*N*-allyloxycarbonyl-L-vancosamine as a green oil (3.61 g, max. 13.9 mmol). This was then suspended in pyridine (60 mL), after which Ac_2O (10 mL) and a catalytic amount of DMAP were added. After stirring overnight, the reaction was quenched by addition of MeOH (12 mL) and concentrated *in vacuo*. The residue was partitioned between EtOAc and 1M HCl, after which the organic layer was washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (10:90 EtOAc:pentane) gave the title compound as a clear thick oil (2.53 g, 8.40 mmol, 57% over 3 steps from vancomycin hydrochloride **30**). Spectral data was in accordance with that of literary precedence.[20,21]

Phenyl 3-*N*-allyloxycarbonyl-4-*O*-acetyl-1-thio-L-vancosamine (32)[20]



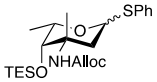
31 (2.53 g, 8.4 mmol) was coevaporated from toluene, after which it was dissolved in DCM (100 mL). Activated molecular sieves (4Å) were added and the mixture was allowed to stir for 30 minutes. It was then cooled down to 0°C, after which thiophenol (0.90 mL, 8.8 mmol, 1.05 eq) and $BF_3{\cdot}OEt_2$ (1.14 mL, 9.24 mmol, 1.1 eq) were added dropwise and the mixture was allowed to warm up to RT. Over the course of 5 hours, an additional such portion of $BF_3{\cdot}OEt_2$ was added. The mixture was then filtered and poured onto sat. aq. $NaHCO_3$. The aqueous layer was extracted with DCM, and the combined organic layers were washed with 1M NaOH and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (10:90 EtOAc:pentane) gave the title compound as a white solid (2.64 g, 6.96 mmol, 83%). Spectral data was in accordance with that of literary precedence.[20]

Phenyl 3,4-carbamoyl-1-thio-L-vancosamine (33)



To a solution of **32** (2.64 g, 6.96 mmol) in MeOH (55 mL) was added NaOMe until pH>10. The reaction was stirred for 2.5 hours, after which it was quenched by addition of dry ice and concentrated *in vacuo*. Column chromatography (15:85 – 100:0 EtOAc:pentane) gave the title compound as a colourless oil (1.70 g, 6.09 mmol, 88%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.50 (ddt, *J* = 8.1, 5.0, 1.1 Hz, 3H), 7.40 – 7.17 (m, 7H), 6.14 (s, 1H), 6.00 (s, 1H), 5.50 (dd, *J* = 10.3, 6.2 Hz, 1H), 4.63 (dd, *J* = 11.4, 2.3 Hz, 1H), 4.23 – 4.02 (m, 2H), 3.85 (d, *J* = 2.0 Hz, 1H), 3.77 (qd, *J* = 6.5, 2.1 Hz, 1H), 2.25 (dd, *J* = 15.2, 6.2 Hz, 1H), 2.11 (dd, *J* = 13.5, 2.2 Hz, 1H), 1.95 (dd, *J* = 13.5, 11.4 Hz, 1H), 1.75 (dd, *J* = 15.2, 10.4 Hz, 1H), 1.49 – 1.37 (m, 9H), 1.30 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7, 158.6, 134.2, 133.5, 132.2, 132.0, 129.1, 127.9, 127.7, 82.8, 81.3, 81.1, 80.7, 70.7, 64.8, 56.6, 55.5, 41.6, 35.8, 29.0, 23.3, 17.1, 15.8. HRMS: $(M + H)^+$ calculated for $C_{14}H_{18}NO_3S$ 280.1007; found 280.1000.

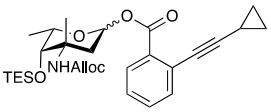
Phenyl 3-*N*-allyloxycarbonyl-4-*O*-triethylsilyl-1-thio-L-vancosamine (34)



A solution of **33** (852 mg, 3.05 mmol) in 1M NaOH (61 mL) was refluxed for 6 hours, after which it was extracted thrice with DCM. The organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude amine was redissolved in THF/H_2O (1:1 v/v, 30 mL) after which $NaHCO_3$ (513 mg, 6.1 mmol, 2 eq) and allyloxycarbonyl succinimide (975 mg, 4.88 mmol, 1.6 eq) was added. After stirring for 3 days, it was partitioned between EtOAc and brine. The aqueous layer was extracted with EtOAc and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude alcohol was redissolved in DCM (33 mL), after which pyridine (0.8 mL, 11.9 mmol, 3.9 eq) and triethylsilyl triflate (1.34 mL, 6.1 mmol, 2 eq) were added at 0°C. After stirring at that temperature for 15 minutes, the reaction mixture was diluted

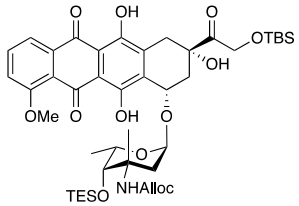
with EtOAc. It was then washed with aq. sat. $NaHCO_3$, H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (4:96 – 10:90 Et_2O:pentane) gave the title compound as a colourless oil (1.24 g, 2.75 mmol, 90% over 3 steps). ^1H NMR (500 MHz, Chloroform-*d*) δ 7.62 – 7.43 (m, 4H), 7.43 – 7.16 (m, 6H), 6.03 – 5.77 (m, 2H), 5.38 – 5.15 (m, 6H), 4.96 – 4.82 (m, 2H), 4.59 – 4.45 (m, 4H), 4.27 – 4.13 (m, 1H), 3.85 – 3.74 (m, 1H), 3.64 (dd, *J* = 4.8, 1.2 Hz, 1H), 3.54 (s, 1H), 3.09 (d, *J* = 14.1 Hz, 1H), 2.00 – 1.86 (m, 2H), 1.66 (dd, *J* = 14.2, 9.3 Hz, 1H), 1.45 (s, 3H), 1.29 (dd, *J* = 6.9, 1.2 Hz, 3H), 1.27 (dd, *J* = 6.4, 1.2 Hz, 3H), 0.98 (tdd, *J* = 7.9, 4.2, 1.5 Hz, 27H), 0.70 – 0.50 (m, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.0, 133.0, 131.7, 131.2, 128.9, 128.8, 127.2, 127.1, 117.6, 80.5, 75.1, 74.0, 72.4, 65.2, 55.5, 37.5, 18.7, 14.8, 7.2, 7.0, 6.7, 5.9, 5.5, 5.2. HRMS: $(M + Na)^+$ calculated for $C_{23}H_{37}NO_4SSiNa$ 474.2110; found 474.2105.

_o_-Cyclopropylethynylbenzoyl-3-_N_-allyloxycarbonyl-4-_O_-triethylsilyl-L-vancosamine (35)



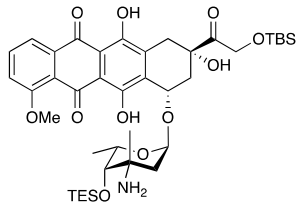
To a solution of **34** (635 mg, 1.41 mmol) in THF/H_2O (10:1 v/v, 24 mL) were added 2,6-lutidine (0.49 mL, 4.23 mmol, 3 eq) and $AgNO_3$ (838 mg, 4.94 mmol, 3.5 eq) and the mixture was stirred in the dark overnight. It was then diluted with EtOAc (200 mL), Na_2SO_4 was added and the mixture was allowed to stir for 40 minutes. This was filtered and concentrated *in vacuo*. Column chromatography (30:70 EtOAc:pentane) gave the crude lactol. To a solution this in DCM (33 mL) were then added DMAP (177 mg, 1.41 mmol, 1 eq), DIPEA (2.3 mL, 12.7 mmol, 9 eq), EDCI.HCl (883 mg, 4.61 mmol, 3.3 eq) and freshly prepared *o*-cyclopropylethynylbenzoic acid **20** (847 mg, 4.23 mmol, 3 eq) and the mixture was stirred overnight. The reaction mixture was partitioned between sat. aq. $NaHCO_3$ and DCM, and the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (6:94 – 20:80 Et_2O:pentane) gave the title compound as a colourless oil (340 mg, 0.644 mmol, 45% over 2 steps, α:β 1:11). Spectral data for the β-anomer: ^1H NMR (500 MHz, Chloroform-*d*) δ 7.92 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.47 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.40 (td, *J* = 7.6, 1.4 Hz, 1H), 7.33 – 7.19 (m, 1H), 6.11 (dd, *J* = 8.6, 2.8 Hz, 1H), 5.90 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.35 – 5.13 (m, 2H), 5.07 (s, 1H), 4.50 (dt, *J* = 5.6, 1.5 Hz, 2H), 3.99 (qd, *J* = 6.5, 2.0 Hz, 1H), 3.59 (d, *J* = 2.0 Hz, 1H), 2.25 (dd, *J* = 12.7, 8.6 Hz, 1H), 2.14 – 2.03 (m, 1H), 1.60 (s, 3H), 1.51 (tt, *J* = 7.6, 6.4 Hz, 1H), 1.31 (d, *J* = 6.5 Hz, 3H), 1.00 (d, *J* = 7.9 Hz, 9H), 0.91 – 0.85 (m, 4H), 0.70 (qd, *J* = 7.9, 1.3 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.6, 134.4, 131.9, 131.2, 130.8, 127.0, 125.2, 117.6, 99.8, 91.9, 74.7, 74.1, 70.8, 65.2, 54.9, 36.2, 18.0, 9.0, 9.0, 7.2, 5.4, 0.8. HRMS: $(M + Na)^+$ calculated for $C_{29}H_{41}NO_6SiNa$ 550.2601; found 550.2593.

7-[3-_N_-allyloxycarbonyl-4-_O_-triethylsilyl-α-L-vancosamino]-14-O-tert-butyldimethylsilyl-doxorubicinone (36)



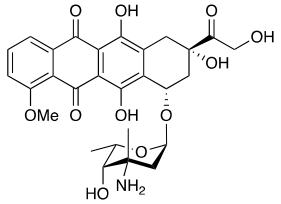
To a solution of donor **35** (330 mg, 0.625 mmol) and 14-*O*-*tert*-butyldimethylsilyl-doxorubicinone **22** (496 mg, 0.938 mmol, 1.5 eq) in DCM (12.5 mL), activated molecular sieves (4Å) were added. The mixture was stirred for 30 minutes. Subsequently, a freshly prepared 0.1M DCM solution of PPh_3AuNTf_2 (prepared by stirring 1:1 PPh_3AuCl and $AgNTf_2$ in DCM for 30 minutes) (0.63 mL, 0.1 eq) in DCM was added dropwise. After stirring at room temperature for 80 minutes, the mixture was filtered and concentrated *in vacuo*. Column chromatography (10:90 Et_2O:pentane – 1:99 - 10:90 acetone:toluene) of the residue gave the title compound (262 mg, 0.301 mmol, 48%), in addition to an α/β mixture (100 mg, 0.115 mmol, 20%). Total yield as a red solid (362 mg, 0.446 mmol, 68%, α:β 6:1). ^1H NMR (500 MHz, Chloroform-*d*) δ 13.83 (s, 1H), 13.14 (s, 1H), 7.94 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.72 (dd, *J* = 8.4, 7.7 Hz, 1H), 7.36 (dd, *J* = 8.6, 1.1 Hz, 1H), 5.92 (ddt, *J* = 17.2, 10.4, 5.5 Hz, 1H), 5.44 (t, *J* = 4.6 Hz, 1H), 5.34 – 5.21 (m, 2H), 5.20 (td, *J* = 2.5, 1.2 Hz, 2H), 5.11 (s, 1H), 4.99 – 4.84 (m, 2H), 4.60 (s, 1H), 4.54 – 4.51 (m, 2H), 4.12 (qd, *J* = 6.6, 2.6 Hz, 1H), 4.07 (s, 3H), 3.66 (d, *J* = 2.6 Hz, 1H), 3.19 – 2.77 (m, 2H), 2.48 – 2.36 (m, 2H), 2.14 (dd, *J* = 14.7, 4.1 Hz, 1H), 1.65 (dd, *J* = 14.0, 4.4 Hz, 1H), 1.46 (s, 3H), 1.29 (d, *J* = 6.6 Hz, 3H), 1.01 (t, *J* = 7.9 Hz, 9H), 0.96 (s, 9H), 0.70 (q, *J* = 7.6 Hz, 6H), 0.15 (d, *J* = 4.2 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.7, 186.8, 186.6, 161.1, 156.5, 155.8, 135.7, 135.5, 134.2, 134.0, 133.2, 120.9, 119.8, 118.6, 117.5, 111.4, 111.3, 100.0, 75.1, 69.4, 66.9, 66.8, 65.1, 56.8, 53.5, 36.0, 33.9, 26.0, 18.7, 17.0, 7.1, 5.4, -5.2. HRMS: $(M + Na)^+$ calculated for $C_{44}H_{63}NO_{13}Si_2Na$ 892.3736; found 892.3729.

7-[4-*O*-triethylsilyl-α-L-vancosamino]-14-O-tert-butyldimethylsilyl-doxorubicinone (37)



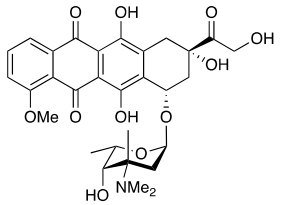
A solution of **36** (252 mg, 0.290 mmol) and *N,N*-dimethylbarbituric acid (202 mg, 1.31 mmol, 4.5 eq) in DCM (29 mL) was degassed for 5 minutes. Then, $Pd(PPh_3)_4$ (17 mg, 0.073 mmol, 0.025 eq) was added and the mixture was allowed to stir for 20 minutes. It was then directly subjected to column chromatography (pentane, then 0:100 – 20:80 acetone:toluene) followed by size-exclusion chromatography (Sephadex LH-20, eluent DCM:MeOH, 1:1) gave the title compound as a red solid (175 mg, 0.223 mmol, 77%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.91 (d, *J* = 7.6 Hz, 1H), 7.72 (t, *J* = 8.1 Hz, 1H), 7.38 – 7.33 (m, 1H), 5.48 (dd, *J* = 5.1, 2.0 Hz, 1H), 5.15 (dd, *J* = 4.3, 2.1 Hz, 1H), 4.95 – 4.79 (m, 2H), 4.52 (s, 1H), 4.18 – 3.94 (m, 4H), 3.34 (s, 1H), 3.19 – 2.70 (m, 3H), 2.33 (dt, *J* = 14.7, 2.1 Hz, 1H), 2.14 (dd, *J* = 14.7, 4.2 Hz, 1H), 1.89 (dd, *J* = 14.0, 5.0 Hz, 1H), 1.60 (d, *J* = 13.9 Hz, 1H), 1.28 (d, *J* = 6.5 Hz, 3H), 1.20 (s, 3H), 1.02 (t, *J* = 8.0 Hz, 9H), 0.96 (s, 9H), 0.72 (q, *J* = 7.8 Hz, 6H), 0.15 (d, *J* = 4.3 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.5, 186.7, 186.4, 161.0, 156.5, 155.6, 135.6, 135.3, 134.1, 134.0, 120.7, 119.7, 118.5, 111.2, 111.2, 100.9, 69.5, 66.6, 66.1, 56.7, 35.8, 33.8, 25.9, 18.7, 17.9, 7.2, 5.6, -5.2, -5.3. HRMS: $(M + H)^+$ calculated for $C_{40}H_{60}NO_{11}Si_2$ 786.3705 found 786.3695.

7-[α-L-Vancosamino]-doxorubicinone (6)



To a solution of **37** (35.0 mg, 44.6 µmol) in pyridine (4.5 mL) in a PTFE tube, was added HF·pyr complex (70 wt% HF, 350 µL) at 0°C. After 45 minutes of stirring at room temperature, solid $NaHCO_3$ was added to quench and the mixture was stirred until cessation of effervescence. It was then filtered off and concentrated *in vacuo*. Column chromatography on neutral silica (DCM – 20:80 MeOH:DCM) gave the title compound as a red solid (22.2 mg, 39.8 µmol, 89%). ^{1}H NMR (500 MHz, Pyridine-d_5) δ 8.03 (d, *J* = 7.6 Hz, 1H), 7.71 (t, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 6.89 (s, 1H), 5.80 (d, *J* = 4.7 Hz, 1H), 5.43 (s, 2H), 5.34 (dd, *J* = 5.1, 2.4 Hz, 1H), 4.76 (q, *J* = 6.5 Hz, 1H), 3.96 (s, 3H), 3.66 – 3.29 (m, 3H), 2.87 (dt, *J* = 14.3, 2.2 Hz, 1H), 2.46 (dd, *J* = 14.4, 5.1 Hz, 1H), 2.38 (dd, *J* = 13.9, 4.9 Hz, 1H), 2.08 (d, *J* = 13.7 Hz, 1H), 1.68 (s, 3H), 1.53 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (126 MHz, Pyr) δ 215.6, 187.4, 187.3, 161.9, 157.7, 156.2, 121.5, 120.0, 119.8, 112.2, 111.7, 102.3, 76.8, 75.6, 70.8, 66.2, 66.1, 57.1, 51.7, 39.4, 37.9, 33.9, 27.0, 18.5. HRMS: $(M + H)^+$ calculated for $C_{28}H_{32}NO_{11}$ 558.1975; found 558.1971.

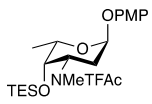
7-[3-Dimethylamino-α-L-vancosamino]-doxorubicinone (7)



A solution of **37** (72.0 mg, 91.6 µmol) in EtOH (23.2 mL) and 37% aq. CH_2O (204 µL, 30 eq) was stirred for 3 hours, before addition of $NaBH(OAc)_3$ (37.9 mg, 0.179 mmol, 1.95 eq). The mixture was stirred for a further 2.5 hours before being poured into sat. aq. $NaHCO_3$. This was extracted with DCM, washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography (10:90 – 30:70 acetone:toluene) gave a crude product which was redissolved in DCM (5.5 mL), to which allyloxycarbonylsuccinimide (90 mg, 0.46 mmol, 5 eq) was added. After stirring overnight, the mixture was concentrated *in vacuo*. Column chromatography (5:95 – 20:80 acetone:toluene) gave the dimethylated amine as a red solid (37 mg, 0.045 mmol, 50%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 13.88 (s, 1H), 13.16 (s, 1H), 7.96 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.74 (t, *J* = 8.1 Hz, 1H), 7.38 (d, *J* = 8.6 Hz, 1H), 5.52 (dd, *J* = 5.1, 2.0 Hz, 1H), 5.15 (dd, *J* = 4.2, 2.0 Hz, 1H), 4.99 – 4.83 (m, 2H), 4.59 (s, 1H), 4.08 (s, 3H), 3.97 (q, *J* = 6.5 Hz, 1H), 3.48 (s, 1H), 3.10 (dd, *J* = 18.7, 2.0 Hz, 1H), 2.84 (d, *J* = 18.7 Hz, 1H), 2.44 (dt, *J* = 14.7, 2.1 Hz, 1H), 2.12 (dd, *J* = 14.7, 4.2 Hz, 1H), 2.06 (s, 6H), 2.00 (dd, *J* = 13.6, 5.0 Hz, 1H), 1.55 (d, *J* = 13.6 Hz, 1H), 1.35 – 1.22 (m, 6H), 0.98 (d, *J* = 16.4 Hz, 18H), 0.65 (qd, *J* = 7.9, 1.7 Hz, 6H), 0.15 (d, *J* = 3.8 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.8, 187.0, 186.6, 161.1, 156.8, 155.9, 135.8, 135.6, 134.5, 134.3, 121.0, 119.9, 118.5, 111.4, 111.3, 101.7, 73.7, 70.1, 67.3, 66.8, 56.8, 37.7, 36.0, 33.8, 26.1, 18.8, 18.2, 13.4, 7.4, 5.9, -5.2. HRMS: $(M + H)^+$ calculated for $C_{42}H_{64}NO_{11}Si_2$ 814.4018; found 814.4011.

To a solution of the above compound (33.3 mg, 40.9 µmol) in pyridine (4.1 mL) in a PTFE tube, was added HF·pyr complex (70 wt% HF, 320 µL) at 0°C. After 70 minutes of stirring at room temperature, solid $NaHCO_3$ was added to quench and the mixture was stirred until cessation of effervescence. It was then filtered off and partitioned between DCM and H_2O. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography on neutral silica (DCM – 50:50 MeOH:DCM) gave the title compound as a red solid (21.1 mg, 36 µmol, 88%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 13.95 (s, 1H), 13.20 (s, 1H), 8.01 (d, *J* = 7.7 Hz, 1H), 7.78 (t, *J* = 8.1 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 5.57 (d, *J* = 5.2 Hz, 1H), 5.22 (dd, *J* = 4.1, 2.0 Hz, 1H), 4.76 (s, 2H), 4.59 (s, 1H), 4.09 (s, 3H), 3.98 (q, *J* = 6.6 Hz, 1H), 3.55 – 3.13 (m, 3H), 2.95 (d, *J* = 18.7 Hz, 1H), 2.49 – 2.33 (m, 1H), 2.13 (s, 7H), 1.83 (dd, *J* = 14.0, 5.3 Hz, 1H), 1.67 (d, *J* = 13.8 Hz, 1H), 1.41 (d, *J* = 6.5 Hz, 3H), 0.95 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.9, 187.2, 186.8, 161.2, 156.6, 155.8, 135.9, 135.6, 134.1, 133.8, 121.0, 119.9, 118.6, 111.6, 111.5, 101.2, 70.0, 69.7, 65.5, 64.6, 56.8, 56.3, 36.4, 35.9, 35.4, 34.0, 17.9, 12.8. HRMS: $(M + H)^+$ calculated for $C_{30}H_{36}NO_{11}$ 586.228; found 586.2282.

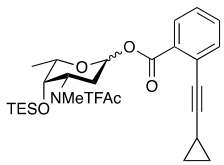
***p*-Methoxyphenyl-3-*N*-methyl-trifluoroacetylamido-2,3-dideoxy-4-triethylsilyl-α-L-fucopyranoside (39)**



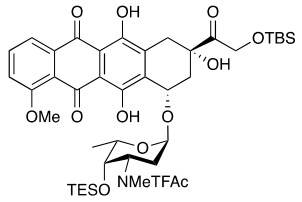
A suspension of **38** (Chapter 3) (638 mg, 1.38 mmol) and K_2CO_3 (3.82 g, 13.8 mmol, 20 eq) in acetone:iodomethane (5:1 v/v, 90 mL) was stirred in a sealed vessel at 50 °C over 3 days. It was then concentrated *in vacuo* and partitioned between DCM and H_2O. The aqueous layer was extracted with DCM and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (5:95 – 10:90 Et_2O:pentane) gave the title compound as a white solid (659 mg, 1.38 mmol, quant.). Spectral data for the major rotamer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, *J* = 7.4 Hz, 2H), 6.82 (d, *J* = 7.7 Hz, 2H), 5.61 (s, 1H), 4.91 (d, *J* = 13.0 Hz, 1H), 4.11 (d, *J* = 6.3 Hz, 1H), 4.04 (s, 1H), 3.77 (s, 3H), 3.14 (s, 3H), 2.54 (t, *J* = 12.8 Hz, 1H), 1.85 (d, *J* = 11.8 Hz, 1H), 1.49 (m, 1H), 1.13 (d, *J* = 6.2 Hz, 3H), 0.98 (t, *J* = 7.5 Hz, 9H), 0.63 (q, *J* = 7.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2, 157.8, 157.5, 157.1, 154.8, 150.9, 117.5, 114.7, 96.1, 71.1, 68.0, 55.7, 53.0, 27.6, 17.6, 7.1, 5.5. HRMS: $[M + H]^+$ calculated for $C_{22}H_{35}F_3NO_5Si$ 478.22311; found 478.22287.

***o*-Cyclopropylethynylbenzoyl-3-*N*-methyl-trifluoroacetylamido-2,3-dideoxy-4-triethylsilyl-L-fucopyranoside (40)**

To a solution of **39** (80 mg, 0.17 mmol) in MeCN:H_2O (1:1 v/v, 4.4 mL) were added NaOAc (140 mg, 1.71 mmol, 10 eq) and $Ag(DPAH)_2.H_2O$ (312 mg, 0.681 mmol, 4 eq) consecutively at 0°C. After stirring for 2 hours at that temperature, the reaction mixture was poured into sat. aq. $NaHCO_3$ and extracted with DCM twice. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give the crude hemiacetal as a yellow solid. To a solution of the above hemiacetal in DCM (1.7 mL) were then added DMAP (21 mg, 0.17 mmol, 1 eq), DIPEA (0.13 mL, 0.77 mmol, 4.5 eq), EDCI·HCl (104 mg, 0.543 mmol, 3.2 eq) and freshly prepared *o*-cyclopropylethynylbenzoic acid **20** (96 mg, 0.51 mmol, 3 eq) and the mixture was stirred overnight. Thereafter, an equal portion of all reagents mentioned above was added again. After stirring another night, the reaction mixture was partitioned between sat. aq. $NaHCO_3$ and DCM, and the organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (5:95 Et_2O:pentane) gave the title compound as a white solid (64 mg, 0.12 mmol, 70%, 1:5 α:β). Spectral data for the β-anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.51 – 7.46 (m, 1H), 7.43 (td, *J* = 7.6, 1.3 Hz, 1H), 7.31 (td, *J* = 7.4, 6.9, 5.2 Hz, 1H), 6.01 (dd, *J* = 9.5, 2.1 Hz, 1H), 4.46 (dt, *J* = 13.7, 3.4 Hz, 1H), 3.98 (s, 1H), 3.80 (q, *J* = 6.3 Hz, 1H), 3.16 (s, 3H), 2.43 (ddd, *J* = 13.7, 11.1, 9.7 Hz, 1H), 1.95 (dt, *J* = 11.2, 2.6 Hz, 1H), 1.54 – 1.49 (m, 1H), 1.27 (d, *J* = 6.5 Hz, 3H), 0.98 (t, *J* = 7.9 Hz, 9H), 0.92 – 0.88 (m, 4H), 0.68 – 0.59 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 158.1, 157.8, 157.4, 157.1, 134.4, 132.2, 130.9, 130.7, 127.1, 125.2, 118.0, 115.1, 99.9, 94.0, 74.6, 73.7, 70.0, 56.2, 32.3, 28.4, 17.6, 9.0, 7.1, 5.4, 0.8. Spectral data for the α-anomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 – 8.08 (m, 1H), 7.93 (td, *J* = 8.8, 8.4, 2.6 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.42 – 7.37 (m, 1H), 6.59 (s, 1H), 4.86 (ddd, *J* = 13.7, 3.8, 2.4 Hz, 1H), 4.34 (q, *J* = 6.6 Hz, 1H), 4.13 (s, 1H), 3.16 (s, 3H), 2.65 (td, *J* = 13.2, 3.5 Hz, 1H), 1.94 – 1.88 (m, 1H), 1.65 – 1.59 (m, 1H), 1.28 (s, 3H), 0.92 (dq, *J* = 6.3, 2.3 Hz, 9H), 0.89 – 0.80 (m, 4H), 0.66 (qd, *J* = 7.9, 3.3 Hz, 6H). HRMS: $[M + Na]^+$ calculated for $C_{27}H_{36}F_3NO_5SiNa$ 562.22071; found 562.22058.

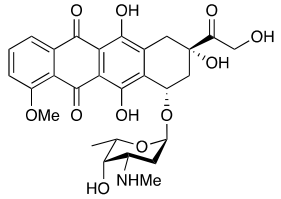


7-[3-*N*-methyl-trifluoroacetylamido-2,3-dideoxy-4-triethylsilyl-L-fucopyranoside]-14-O-tert-butyldimethylsilyl-doxorubicinone (41)



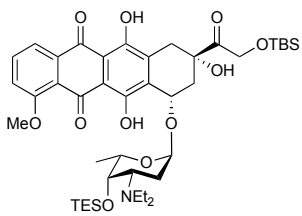
14-O-TBS-doxorubicinone **22** (560 mg, 1.06 mmol, 2 eq) and donor **40** (286 mg, 0.530 mmol, 1 eq) were coevaporated thrice with toluene and then dissolved in DCM (10.6 mL), after which freshly activated 4 Å molecular sieves were added, and stirred for 30 minutes, whereupon freshly prepared PPh_3AuNTf_2 (0.05 M solution in DCM, 1.06 mL, 0.1 eq) was added. After stirring for 5 minutes, the resulting solution was diluted with DCM, filtered over Celite and concentrated *in vacuo*. Purification by column chromatography (10:90 EtOAc:pentane and then 3:97 acetone:toluene) gave the title compound as a red solid (330 mg, 0.374 mmol, 71%). Spectral data for the major rotamer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.96 (s, 1H), 13.19 (s, 1H), 8.01 (d, *J* = 7.6 Hz, 1H), 7.77 (t, *J* = 8.1 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 5.60 (d, *J* = 3.3 Hz, 1H), 5.28 – 5.19 (m, 1H), 4.97 – 4.84 (m, 2H), 4.42 (d, *J* = 12.7 Hz, 1H), 4.28 (s, 1H), 4.09 (s, 3H), 4.02 (s, 1H), 3.18 (d, *J* = 18.8 Hz, 1H), 3.04 (s, 3H), 2.91 (d, *J* = 18.7 Hz, 1H), 2.43 (td, *J* = 13.2, 4.0 Hz, 1H), 2.35 (d, *J* = 14.9 Hz, 1H), 2.20 (dd, *J* = 14.8, 4.1 Hz, 1H), 1.68 (dd, *J* = 12.2, 3.7 Hz, 1H), 1.64 (s, 1H), 1.21 (d, *J* = 6.5 Hz, 3H), 1.04 – 0.90 (m, 18H), 0.70 – 0.53 (m, 6H), 0.16 (d, *J* = 2.9 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.6, 187.2, 186.7, 161.1, 156.5, 155.9, 135.9, 135.6, 134.3, 133.9, 120.9, 120.0, 118.5, 111.5, 111.4, 101.2, 70.9, 70.7, 68.5, 66.9, 56.8, 53.1, 35.9, 34.0, 27.2, 26.0, 7.1, 5.5. HRMS: $[M + Na]^+$ calculated for $C_{42}H_{58}F_3NO_{12}Si_2Na$ 904.33418; found 904.33459.

***N*-methyl-doxorubicin (8)**



To a solution of **41** (101 mg, 0.115 mmol) in pyridine (4.5 mL) and Et_3N (2.25 mL) was added triethylamine trihydrofluoride (2.25 mL). After stirring for 1 h, it was poured into sat. aq. $NaHCO_3$. The organic layer was separated and thrice washed with sat. aq. $NaHCO_3$ after which it was dried over Na_2SO_4 and concentrated *in vacuo*. The resulting acetamide was dissolved in MeOH (9 mL), to which NaOMe (17 mg, 0.29 mmol, 2.5 eq) was added, rendering the solution blue. After 20 minutes, dry ice was added until the red colour had returned and the mixture was poured into brine. This was then repetitively extracted with $CHCl_3$, dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography on neutral silica (10:90 – 20:80 MeOH:DCM) gave the title compund as a red solid (15 mg, 26 µmol, 23% over 2 steps). ^{1}H NMR (500 MHz, MeOD) δ 7.87 – 7.67 (m, 2H), 7.60 – 7.40 (m, 1H), 5.44 (s, 1H), 4.97 (s, 1H), 4.79 – 4.69 (m, 2H), 4.26 (q, *J* = 6.4 Hz, 1H), 4.00 (s, 3H), 3.84 (s, 1H), 3.49 (ddd, *J* = 11.3, 5.9, 2.8 Hz, 1H), 3.00 (d, *J* = 18.6 Hz, 1H), 2.80 (d, *J* = 18.5 Hz, 1H), 2.64 (s, 3H), 2.32 (d, *J* = 14.7 Hz, 1H), 2.12 (dd, *J* = 14.6, 4.7 Hz, 1H), 2.05 – 1.97 (m, 3H), 1.31 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (126 MHz, MeOD) δ 214.84, 187.83, 187.58, 162.41, 157.24, 156.00, 137.24, 136.13, 135.48, 135.12, 121.31, 120.47, 112.32, 112.06, 100.96, 76.99, 71.31, 67.82, 66.01, 65.67, 57.13, 56.15, 49.51, 49.34, 49.17, 49.00, 48.83, 48.66, 48.49, 37.23, 33.65, 30.35, 28.28, 16.97. HRMS: $[M + H]^+$ calculated for $C_{29}H_{31}NO_{11}$ 558.19699; found 558.19684.

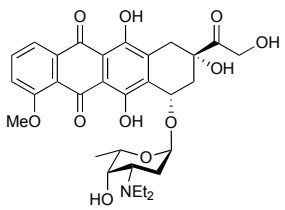
7-[3-Diethylamino-2,3-dideoxy-4-triethylsilyl-L-fucopyranoside]-14-*O*-*tert*-butyldimethylsilyl-doxorubicinone (47)



To a solution of **46** (Chapter 2) (239 mg, 0.300 mmol) in THF/H_2O (25 mL, 1:1, v/v) was added polymer bound PPh_3 (3 mmol/g PPh_3 loading, 667 mg, 2.00 mmol, 6.7 eq) and the reaction mixture was stirred for 3 days at 50°C. Additional polymer bound PPh_3 (500 mg, 1.5 mmol, 5 eq) was added and the reaction mixture was stirred for 3 more days at the same temperature. The reaction mixture was then allowed to cool to room temperature and filtered off, the filtrate was concentrated *in vacuo* and co-evaporated with toluene. Column chromatography (3:97 – 10:90 acetone:toluene) gave the intermediate amine (148 mg, 0.193 mmol, 64%). To a solution of the amine thus obtained (141 mg, 0.183 mmol) in EtOH (15 mL) was added acetaldehyde (50% w/w in EtOH, 1.1 mL, 11 mmol, 60 eq). After stirring for 30 minutes, $NaBH(OAc)_3$ (74 mg, 0.35 mmol, 1.9 eq) was added and the reaction mixture was stirred for 5 hours. Sat aq. $NaHCO_3$ was added and the solution was extracted with DCM thrice. Combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography (4:96 – 5:95 acetone:toluene) afforded the title compound as a red

solid (71 mg, 86 μmol, 30% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.91 (s, 1H), 13.25 (s, 1H), 8.01 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.77 (t, *J* = 8.1 Hz, 1H), 7.45 – 7.36 (m, 1H), 5.53 (d, *J* = 3.8 Hz, 1H), 5.27 (dd, *J* = 4.0, 2.2 Hz, 1H), 4.99 – 4.82 (m, 3H), 4.09 (s, 3H), 3.88 (q, *J* = 6.3 Hz, 1H), 3.73 (s, 1H), 3.18 (dd, *J* = 19.0, 1.9 Hz, 1H), 2.99 (d, *J* = 18.9 Hz, 1H), 2.57 (q, *J* = 6.9 Hz, 5H), 2.36 (dt, *J* = 14.8, 2.2 Hz, 1H), 2.21 – 1.97 (m, 2H, H-8), 1.64 (dd, *J* = 12.8, 3.5 Hz, 1H), 1.31 – 1.18 (m, 6H), 1.07 – 0.92 (m, 18H), 0.88 (t, *J* = 7.0 Hz, 6H), 0.66 (qd, *J* = 8.3, 7.9, 1.7 Hz, 6H), 0.14 (d, *J* = 2.8 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 211.6, 187.2, 186.8, 161.1, 156.6, 156.0, 135.8, 135.7, 134.5, 134.2, 121.1, 119.9, 118.5, 111.5, 111.4, 101.9, 77.4, 71.1, 69.6, 69.4, 66.8, 56.8, 56.7, 41.9, 35.6, 34.1, 27.8, 26.0, 18.7, 18.2, 11.2, 7.3, 5.6, -5.1, -5.3. HRMS: $(M + H)^+$ calculated for $C_{43}H_{66}NO_{11}Si_2$ 828.4175; found 828.4161.

***N,N*-diethyldoxorubicin (9)**

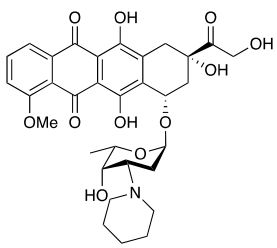


47 (52 mg, 63 μmol) was dissolved in pyridine (2 mL) and cooled to 0°C. HF·pyridine (70 wt% HF, 0.48 mL) was added and the reaction mixture was stirred for 5h at this temperature. Solid $NaHCO_3$ was added to quench and the mixture was stirred until cessation of effervescence. It was then filtered off and the filtrate was diluted with DCM, washed with H_2O and dried over Na_2SO_4. Solvent was removed *in vacuo* and the residue was subjected to column chromatography on neutral silica (0:100 - 15:85 MeOH:DCM) to afford the title compound as a red solid (37 mg, 62 μmol, 98%). ^{1}H NMR (500 MHz, , $CDCl_3$) δ 13.94 (s, 1H), 13.20 (s, 1H), 8.01 (dd, J = 7.7, 1.0 Hz, 1H), 7.79 (dd, J = 8.5, 7.7 Hz, 1H), 7.41 (dd, J = 8.6, 1.1 Hz, 1H), 5.56 (d, J = 2.7 Hz, 1H), 5.30 (dd, J = 4.0, 2.1 Hz, 1H), 4.83 (s, 1H), 4.77 (s, 2H), 4.10 (s, 3H), 4.03 – 3.87 (m, 1H), 3.69 (t, J = 1.9 Hz, 1H), 3.23 (dd, J = 18.8, 2.0 Hz, 1H), 2.97 (d, J = 18.8 Hz, 1H), 2.74 – 2.57 (m, 5H), 2.39 (dt, J = 14.6, 2.2 Hz, 1H), 2.16 (dd, J = 14.7, 4.0 Hz, 1H), 1.97 – 1.67 (m, 2H), 1.40 (d, J = 6.6 Hz, 3H), 0.96 (t, J = 7.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.9, 187.2, 186.8, 161.2, 156.4, 155.8, 135.9, 135.6, 134.0, 133.7, 120.9, 119.9, 118.6, 111.6, 111.5, 101.1, 76.9, 69.6, 67.2, 66.2, 65.6, 56.8, 55.2, 41.6, 35.5, 34.1, 28.3, 17.4, 11.1. HRMS: $(M + H)^+$ calculated for $C_{31}H_{38}NO_{11}$ 600.2445; found 600.2439.

General Procedure A: *N*-cyclic doxorubicins

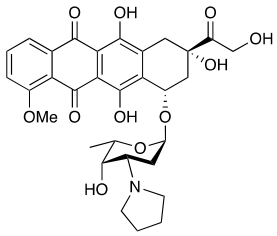
To a solution of doxorubicin·HCl in DMF (0.033M) were added triethylamine (3 eq) and the corresponding diiodoalkane or diiodoether (18 eq). The mixture was allowed to stir for 5 days, or until LCMS showed disappearance of the starting material. It was then poured into H_2O, extracted with $CHCl_3$ repetitively, dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography on neutral silica (MeOH:DCM) gave the title compounds as red solids.

***N*-piperidinodoxorubicin (10)**



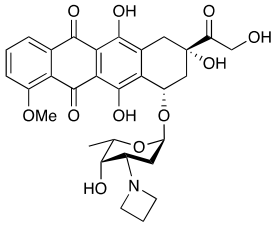
Prepared according to General Procedure A from doxorubicin·HCl (100 mg) and diiodopentane to give the title compound as a red solid (81 mg, 0.13 mmol, 77%). ^{1}H NMR (500 MHz, Chloroform-d_3) δ 14.63 (s, 1H), 13.57 (s, 1H), 8.17 – 8.01 (m, 1H), 7.77 (t, *J* = 8.1 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 1H), 5.89 (d, *J* = 3.5 Hz, 1H), 5.61 (d, *J* = 20.0 Hz, 1H), 5.53 – 5.39 (m, 2H), 4.79 (q, *J* = 6.6 Hz, 1H), 4.46 (s, 1H), 3.98 (s, 3H), 3.66 – 3.36 (m, 6H), 3.23 (t, *J* = 6.9 Hz, 1H), 2.88 (dt, *J* = 14.5, 2.3 Hz, 1H), 2.59 (dd, *J* = 14.5, 5.3 Hz, 1H), 2.46 (dh, *J* = 17.0, 3.8 Hz, 2H), 1.81 (dtt, *J* = 11.1, 8.1, 4.6 Hz, 1H), 1.74 – 1.57 (m, 4H), 1.53 (d, *J* = 6.5 Hz, 3H), 1.44 (p, *J* = 7.5 Hz, 1H), 1.40 – 1.22 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.8, 187.6, 161.9, 157.6, 156.1, 121.5, 120.0, 112.2, 111.9, 101.1, 76.9, 70.9, 68.3, 66.5, 66.4, 62.0, 57.2, 53.9, 51.1, 37.9, 34.2, 28.0, 24.4, 17.9, 8.3, 7.8. HRMS: $[M + H]^+$ calculated for $C_{32}H_{38}NO_{11}$ 612.2445; found 612.2242.

***N*-pyrrolidinodoxorubicin (11)**



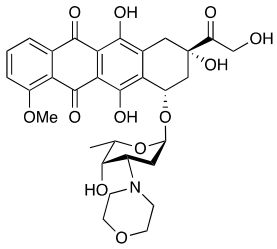
Prepared according to General Procedure A from doxorubicin·HCl (50 mg) and diiodopropane to give the title compound as a red solid (27 mg, 45 µmol, 53%). HRMS: $[M + H]^+$ calculated for $C_{31}H_{36}NO_{11}$ 598.2288; found 598.2291.

***N*-azetidinodoxorubicin (12)**



Prepared according to General Procedure A from doxorubicin·HCl (50 mg) and diiodopropane to give the title compound as a red solid (17 mg, 29 µmol, 34%). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.81 – 7.57 (m, 2H), 7.41 (d, *J* = 8.0 Hz, 1H), 5.39 (d, *J* = 3.6 Hz, 1H), 4.78 – 4.62 (m, 2H), 4.15 (q, *J* = 6.6 Hz, 1H), 3.94 (d, *J* = 17.7 Hz, 7H), 3.69 (d, *J* = 2.7 Hz, 1H), 3.41 (s, 1H), 2.97 – 2.87 (m, 1H), 2.68 (d, *J* = 18.4 Hz, 1H), 2.34 (p, *J* = 7.8 Hz, 2H), 2.26 (d, *J* = 14.6 Hz, 1H), 2.05 (dd, *J* = 14.6, 4.9 Hz, 1H), 1.87 (dt, *J* = 9.5, 4.6 Hz, 1H), 1.77 (td, *J* = 12.7, 3.9 Hz, 1H), 1.26 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 214.7, 187.6, 187.4, 162.3, 157.2, 155.9, 137.2, 135.9, 135.4, 135.1, 121.1, 120.3, 112.2, 111.9, 100.9, 77.0, 71.1, 67.9, 65.7, 64.7, 62.0, 57.1, 53.5, 37.1, 33.6, 26.5, 17.2, 16.9. HRMS: $[M + H]^+$ calculated for $C_{30}H_{34}NO_{11}$ 584.2132; found 584.2129.

***N*-morpholinodoxorubicin (13)**



Prepared according to General Procedure A from doxorubicin·HCl (50 mg) and bis(2-iodo)ethyl ether to give the title compound as a red solid (32 mg, 52 µmol, 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.95 (s, 1H), 13.20 (s, 1H), 8.01 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.79 (t, *J* = 8.1 Hz, 1H), 7.46 – 7.36 (m, 1H), 5.56 (d, *J* = 3.1 Hz, 1H), 5.28 (dd, *J* = 4.1, 2.1 Hz, 1H), 4.74 (d, *J* = 15.8 Hz, 3H), 4.09 (s, 3H), 3.96 (q, *J* = 6.7 Hz, 1H), 3.71 (dt, *J* = 12.3, 4.1 Hz, 6H), 3.23 (dd, *J* = 18.8, 1.9 Hz, 1H), 2.97 (d, *J* = 18.8 Hz, 1H), 2.49 – 2.32 (m, 4H), 2.17 (dd, *J* = 14.7, 4.1 Hz, 1H), 1.78 (dd, *J* = 11.2, 4.1 Hz, 2H), 1.39 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (101 MHz, MeOD) δ 213.8, 187.2, 186.7, 161.1, 156.4, 155.7, 136.0, 135.5, 133.9, 133.6, 125.6, 120.9, 120.0, 118.6, 111.6, 111.5, 101.1, 70.0, 67.1, 66.9, 65.6, 65.1, 58.8, 56.8, 49.8, 35.6, 34.0, 30.4, 29.8, 27.5, 17.3. HRMS: $[M + H]^+$ calculated for $C_{31}H_{36}NO_{12}$ 614.2238; found 614.2241.

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Chapter 5

Synthesis of glycosyl regio- and stereoisomers of doxorubicin

Introduction

In the search for more potent anthracyclines with fewer side-effects, several thousands of analogs of doxorubicin (**1**) have been isolated from natural sources and prepared by synthetic and chemo-enzymatic approaches.[1,2] In contrast to most doxorubicin analogs, its 4'-epimer epirubicin (**3**, Figure 1) is a clinically approved anthracycline. Compared to doxorubicin, the amine in epirubicin has a lower pK_{aH}, likely because of hydrogen bonding of the resultant ammonium salt with the *cis* 4'-hydroxyl function.[3] Additionally, Pedersen *et al.* have described the orientation of hydroxyl groups on a sugar ring to be of influence on the pK_a of amine groups on aminosugars.

The first reported[4] synthesis of epirubicin was based on glycosylation of a protected acosamine donor to the daunorubicin aglycone (**14a**, Chapter 2), followed by 14-hydroxylation and deprotection.[5] Later efforts involved the direct conversion of doxorubicin to 4-*epi*-doxorubicin (**3**) through a sequence of protection group manipulations, oxidation of the 4'-hydroxyl to the corresponding ketone and stereoselective reduction to provide the epimeric 4'-alcohol followed by final deprotection.[6] Today, clinical grade epirubicin is produced by means of a mutated *Streptomyces peucetius* in a biotechnological process.[7] In the treatment of certain cancers (breast/ovarian cancer, gastric cancer, lung cancer and lymphomas), epirubicin is preferred over doxorubicin as it exhibits higher efficacy and lower cardiotoxicity.

Chapter 3 presented a coherent set of compounds featuring structural elements of doxorubicin (**1**) and aclarubicin (**4**) in which the aglycone, amine/dimethylamine and nature of the sugar chain were varied. In all presented examples, the stereochemistry and substitution pattern (amine at the 3'-position and hydroxyl at the 4'-position) were kept the same as in the two natural products, that is, 2,3-dideoxy-3-amino-L-fucopyranose or daunosamine. This Chapter focuses on the construction of a focused library of anthracyclines that feature regio- and stereoisomeric deoxyfucose analogues. All compounds contain the doxorubicin aglycone and are in line with the strategy presented in Chapter 3, compounds featuring a non-methylated amine are prepared together with their *N,N*-dimethyl substituted counterparts.

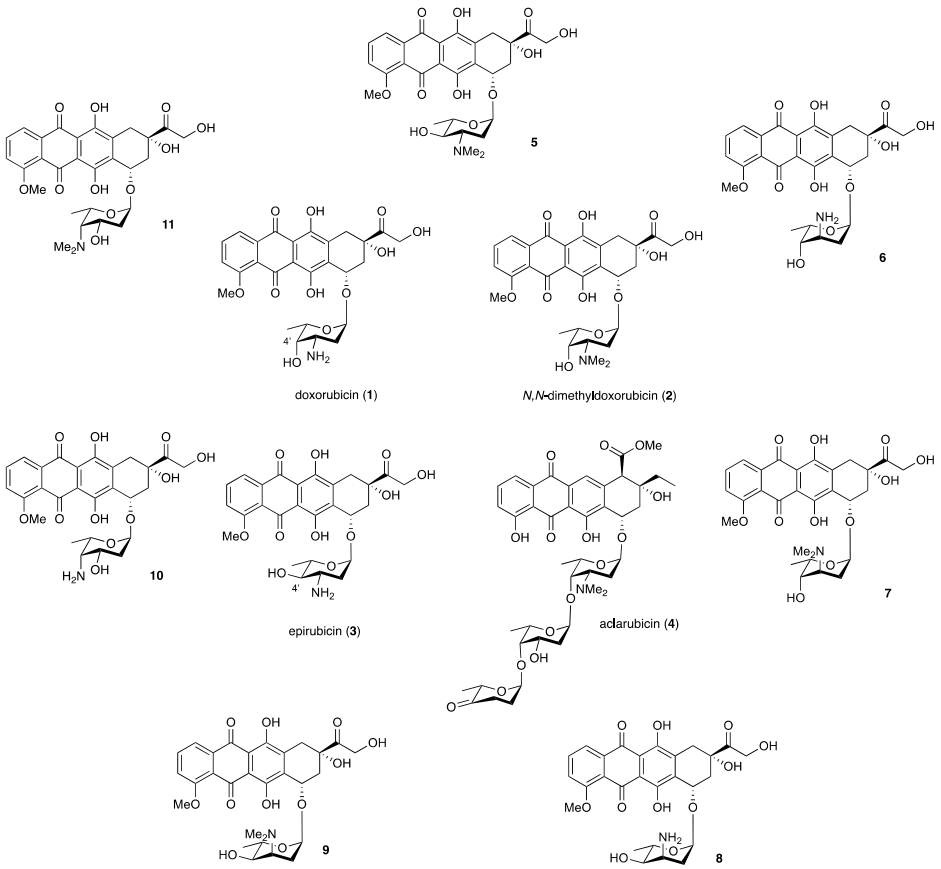
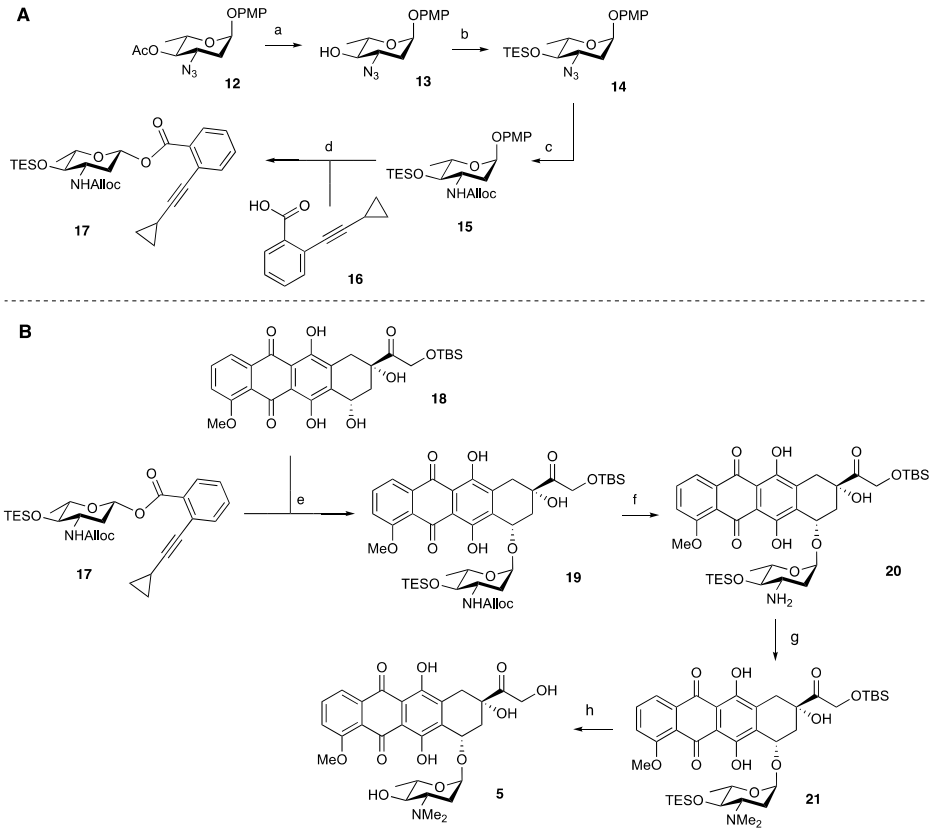


Figure 1. Chemical structures of the doxorubicin derivatives **5**-**11** prepared in this Chapter, differing in stereo- and regiochemistry on the sugar.

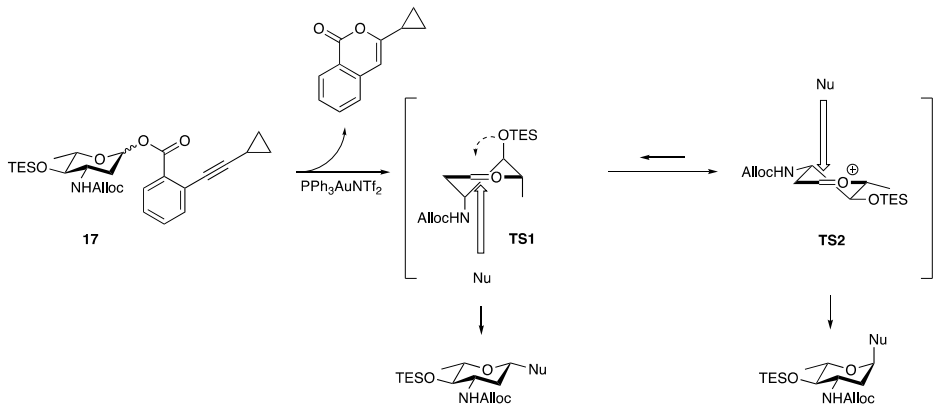
Results and discussion

The synthesis of *N,N*-dimethylepirubicin (**5**), the 4'-epimer of *N,N*-dimethyldoxorubicin (**2**) commenced with orthogonally protected acosamine[8] **12** (Scheme 1A), the synthesis of which is described in Chapter 2. Deprotection of the 4-acetate was followed by triethylsilylation to give **14**. At this stage, the azide was reduced and ensuing carbamoylation with allyl chloroformate provided Alloc-protected amine **15**. Oxidative hydrolysis of the anomeric *p*-methoxyphenolate (using $Ag(DPAH)_2$), followed by Steglich esterification to carboxylic acid **16** provided donor glycoside **17**. Treatment of tetracycle **18** with donor **17** in the presence of catalytic gold(I) yielded anthracycline glycoside **19** in excellent yield (Scheme 1B) and good stereoselectivity (8:1 α:β).



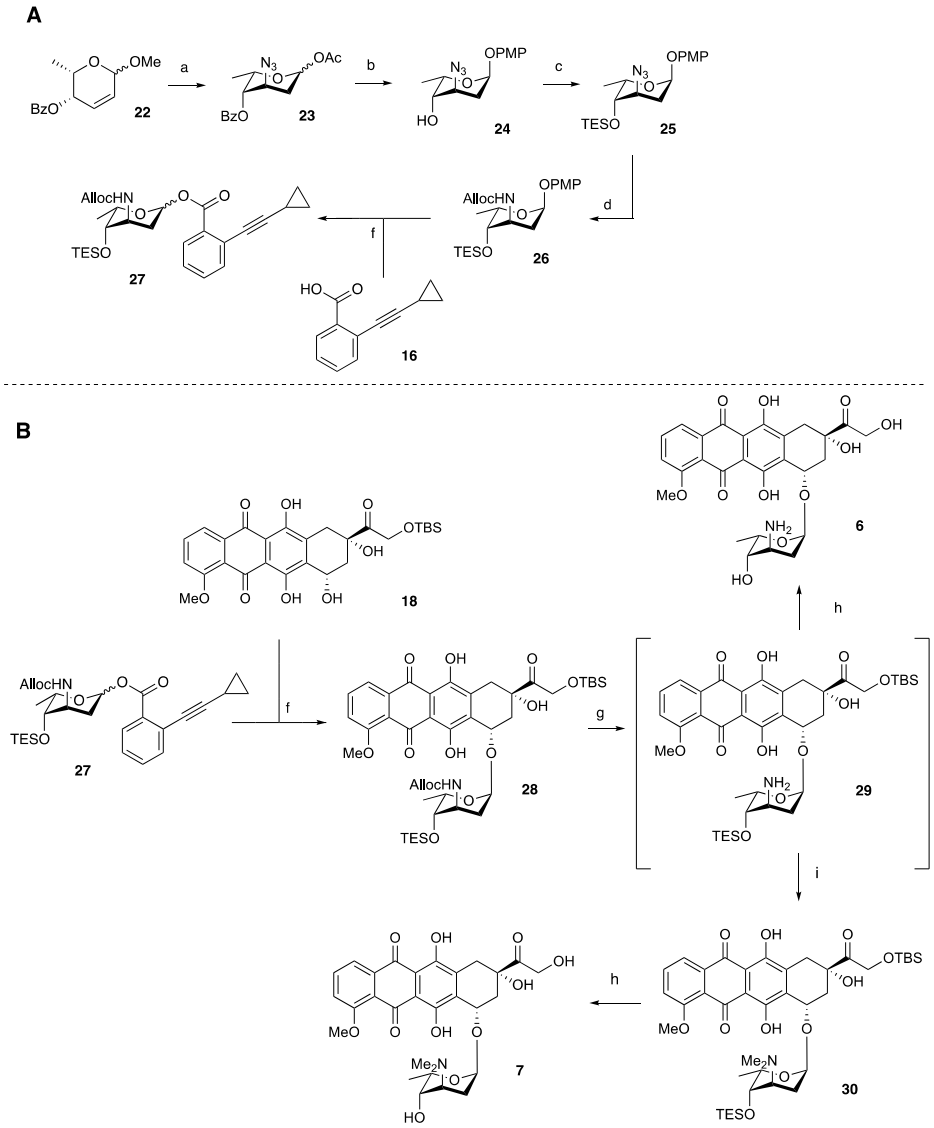
Scheme 1. Synthesis of *N,N*-dimethylepirubicin (**5**). *Reagents and conditions:* (a) NaOMe, MeOH, quant.; (b) TESOTf, pyr., DCM, 95% over 2 steps; (c) *i.* polymer-bound PPh_3, THF, H_2O; *ii.* allyl chloroformate, pyr., DCM, quant. over 2 steps; (d) *i.* $Ag(DPAH)_2{\cdot}H_2O$, NaOAc, MeCN, H_2O, 0 °C; *ii.* EDCI·HCl, DMAP, DIPEA, DCM, 49% over 2 steps (β-adduct only); (e) PPh_3AuNTf_2, DCM, 91% (8:1 α:β); (f) $Pd(PPh_3)_4$, DMBA, DCM, 82%; (g) $NaBH(OAc_3)$, aq. CH_2O, EtOH, 82%; (h) HF·pyr., pyr., 83%.

A mechanistic rationale for the observed selectivity is shown in Scheme 2. Although the 4-silyl ether in TS1 is able to stabilize the positive charge on the oxocarbenium ion, approach of the nucleophile from the bottom face of the ring is hindered by 1,3-diaxial interaction with the 6-methyl group, and the bulky Alloc group on the backside of the ring. The 4-silyl ether in TS2 is unable to stabilize the $^3H_4$ conformation of the reactive intermediate, but approach from the top face can proceed with little hindrance. Long-range participation[9] by the allyloxycarbonyl group can also account for the observed stereoselectivity, but in light of the stereoselectivity observed in the assembly of 3'-epidoxorubicin, *vide infra*, less likely. The desired α-anomer of **19** could be separated by means of column chromatography. Following Pd-mediated removal of the Alloc group to give **20**, reductive dimethylation of the liberated amine took place uneventfully to yield **21**. A final desilylation gave *N,N*-dimethylepirubicin (**5**) in good yield.



Scheme 2. Mechanistic rationale for the stereoselectivity found in the formation of **19**.

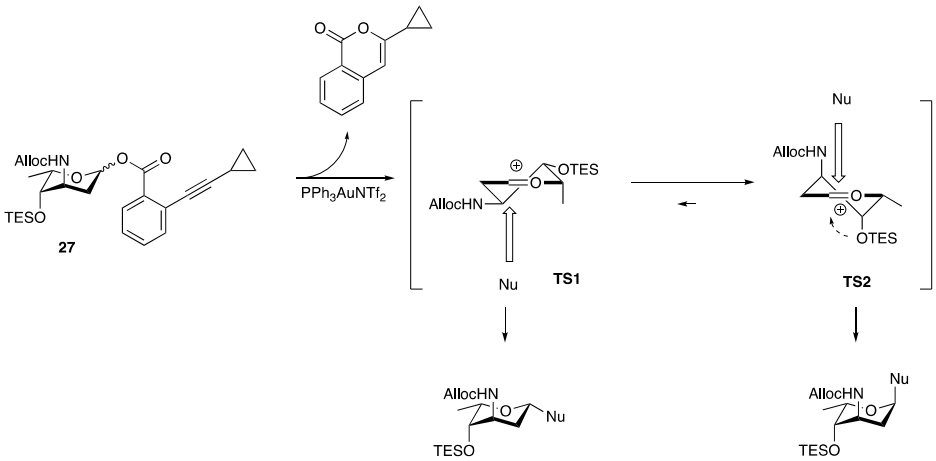
The synthesis of 3'-epi-doxorubicins **6** and **7** commenced with *eno*-pyranoside **22** (Scheme 3A), the construction of which was discussed in Chapter 3. Following the protocol as reported by Renneberg *et al.*[8], exposure of **22** to acidic hydrolysis was followed by 1,4-addition of the azide anion (ca. 2:1 axial:equatorial) to the resulting enal function. Anomeric acetylation gave a mixture from which the desired C3-axial isomer **23** could be isolated. Subjection of this compound together with *p*-methoxyphenol to $BF_3{\cdot}OEt_2$ from -60 °C to -40 °C followed by debenzoylation under Zemplén conditions gave α-glycoside **24**. Silylation of the free alcohol in **24** gave **25** and conversion of the azide in **25** to the corresponding *N*-allyloxycarbamate by means of Staudinger reduction and carbamoylation with allylchloroformate gave **26**.



Scheme 3. Synthesis of 3'-epidoxorubicins (**6**) and (**7**). *Reagents and conditions:* (a) *i.* HCl, THF, H_2O; *ii.* NaN_3, AcOH, THF, H_2O; *iii.* Ac_2O, pyr., DCM, 55% over 3 steps (10:1 α:β); (b) *i. p*-methoxyphenol, $BF_3{\cdot}OEt_2$, DCM, -60 °C to -40 °C; *ii.* NaOMe, MeOH, 77% over 2 steps; (c) TESOTf, pyr., quant.; (d) *i.* PPh_3, THF, H_2O; *ii.* allyl chloroformate, pyr., DCM, -20 °C, quant. over 2 steps; (e) *i.* $Ag(DPAH)_2{\cdot}H_2O$, NaOAc, MeCN, H_2O, 0 °C; *ii.* EDCI·HCl, DMAP, DIPEA, DCM, 79% over 2 steps (1:3 α:β); (f) PPh_3AuNTf_2, DCM, 58% (α only); (g) $Pd(PPh_3)_4$, DMBA, DCM; (h) HF·pyr., pyr., 72% over 2 steps for **5**, 66% for **6**; (i) $NaBH(OAc)_3$, aq. CH_2O, EtOH, 72% over 2 steps.

Silver(II)-mediated oxidation of the anomeric *p*-methoxyphenolate was followed by esterification with *o*-cyclopropylethynylbenzoic acid **16** to give 3-epidaunosamine

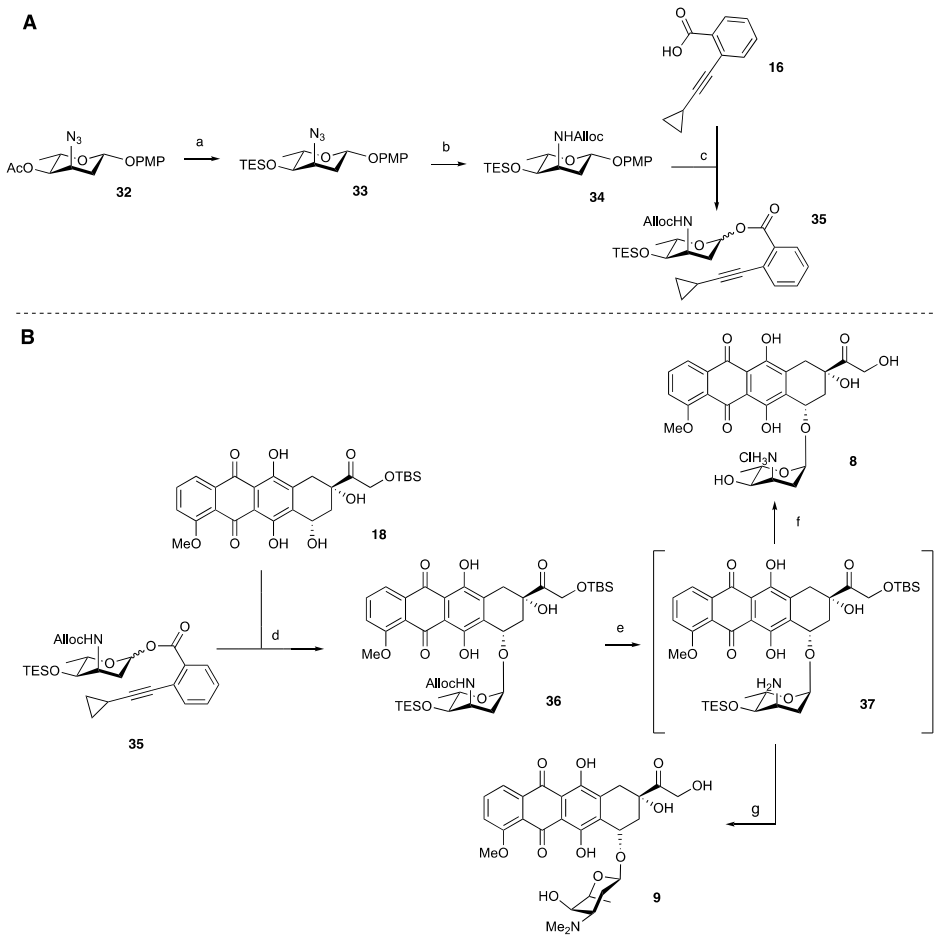
donor **27**. Gold-mediated glycosylation of acceptor **18** with donor **27** proceeded in excellent stereoselectivity to give α-glycoside **28**. Scheme 4 provides a mechanistic rationale for the observed stereoselectivity. In the $^3H_4$ conformation, the incoming nucleophile would encounter 1,3-diaxial interaction with the 6-methyl group. Meanwhile, in the $^4H_3$ half-chair, the silyl ether is able to stabilize the oxocarbenium ion. Since solely α-product is observed, participating properties of the carbamate that would guide formation of the 1,3-*trans* product appear to be insignificant.



Scheme 4. Mechanistic rationale for the 1,3-*cis* stereoselectivity found in the formation of **28**.

Pd-mediated deblocking of the carbamate in **28** gave free amine **29**. Global desilylation gave 3-epidoxorubicin (**6**) in good yield over the two steps. Subjection of amine **29** to reductive amination (CH_2O, $NaBH(OAc)_3$) finished the nogalamine[10] moiety in **30** and a final desilylation yielded *N,N*-dimethyl-3-epidoxorubicin (**7**).

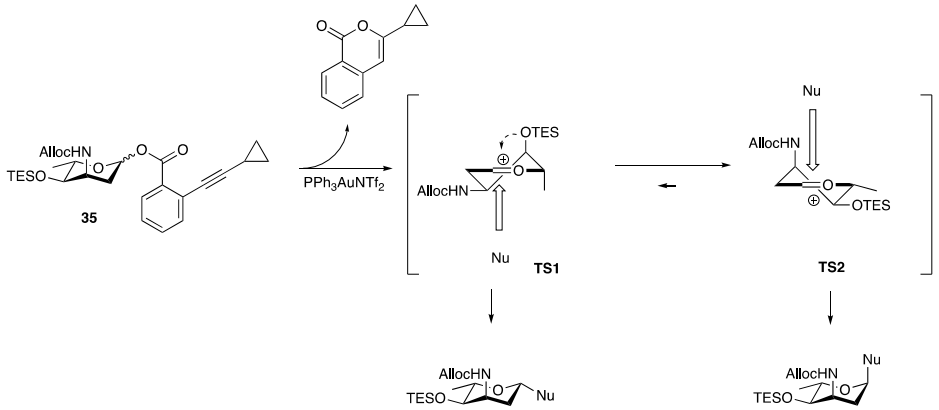
The synthesis of 3'-epi-4'-epidoxorubicins **8** and **9** (Scheme 5A) starts from orthogonally protected β-ristosamine[4] **31**, the construction of which was discussed in Chapter 2. Following procedures similar to those described before in this Chapter, protecting group manipulations yielded orthogonally protected **34**. Liberation of the anomeric *p*-methoxyphenolate and subsequent esterification to **16** gave rise to ristosaminyl glycosyl donor **35**. The envisaged glycosylation to **18** under gold(I)-mediated conditions took place in a non-stereoselective manner and with modest yield. The desired α-configured **36** could be obtained in sufficient quantities and purity nonetheless after by silica gel column chromatography.



Scheme 5. Synthesis of ristosaminyl doxorubicins **8** and **9**. *Reagents and conditions:* (a) *i.* NaOMe, MeOH, quant.; *ii.* TESOTf, pyr., quant.; (b) *i.* PPh_3, THF/H_2O; *ii.* allyl chloroformate, pyr., DCM, -20 °C, 95% over 2 steps; (c) *i.* $Ag(DPAH)_2H_2O$, NaOAc, MeCN, H_2O; *ii.* EDCI·HCl, DMAP, DIPEA, DCM, 57% over 2 steps; (d) PPh_3AuNTf_2, DCM, 50% (1.5:1 α:β); (e) *i.* $Pd(PPh_3)_4$, DMBA, DCM; (f) *i.* HF·pyr., pyr., 0 °C; *ii.* lyophilization from aq. HCl, 54% over 3 steps; (g) *i.* $NaBH(OAc)_3$, aq. CH_2O, EtOH; *ii.* HF·pyr., pyr., 0 °C, 35% over 3 steps.

The poor stereoselectivity of the glycosylation is in line with results reported by as Zeng *et al.* who reported that glycosylations of ristosaminyl alkynylbenzoate donors to various glycosyl acceptors proceeded with variable (2.8:1 – 1:4 α:β) selectivity.[11] As depicted in Scheme 6, the 3-Alloc disfavors α-attack because of unfavorable 1,3-diaxial interactions of this substituent in the $^3H_4$ conformation and the incoming nucleophile. At the same time, the 4-silyl ether is unable to stabilize the oxocarbenium ion in this conformation. Conversely, β-face attack is on the alternative half chair oxocarbenium

ion conformer is hampered by the axial methyl group, although the oxocarbenium can benefit from stabilization of the silyl ether in this constellation.



Scheme 6. Mechanistic rationale for the stereoselectivity found in the formation of **36**.

α-Configured glycoside **36** was subjected to Pd-mediated removal of the Alloc group to obtain free amine **37**. Desilylation followed by lyophilization from aqueous HCl (10 µM, 2 eq) yielded 3,4-epidoxorubicin (or ristosaminyl-doxorubicinone) (**8**). Converting amines **8** and **10** to their hydrochloride salts facilitated in obtaining clear NMR spectra of this compound and did not lead to degradation. Reductive amination onto amine **37** followed by final desilylation yielded the megosaminyl-doxorubicinone (**9**).

Rather than the $^{1}C_4$ conformation observed for **36** and **8**, it was found that **9** takes up the $^{4}C_1$ chair conformation instead. Figure 2 depicts the ^{1}H-spectra of compounds **9** and **36**, annotated with the peak multiplicity and coupling constants of the glycosidic protons. Most notable are the coupling constants found for the anomeric proton in **8**. Whereas in $^{1}C_4$-conformed 2-deoxy fucosides, the anomeric proton typically shows as a doublet (d) with $J_{(H1\text{-}H2ax)}$ = 1-5 Hz, the anomeric proton in **9** instead shows a dd ($J_{(H1\text{-}H2ax)}$ = 8.8 Hz; $J_{(H1\text{-}H2eq)}$ = 4.8 Hz), indicating a trans-diaxial relationship between H1 and $H2_{ax}$. Furthermore, whereas H4 in **36** shows as a dd ($J_{(H4\text{-}H5)}$ = 8.6 Hz; $J_{(H4\text{-}H3)}$ = 4.1 Hz) indicative of a diaxial relationship, H4 in **9** appears as an apparent triplet with a small coupling constant (4.6 Hz), also indicating a $^{4}C_1$-conformer. Finally, the large *J*-value expected for H5 as in **36** is absent in **9**, as H5 shows as a dq ($J_{(H5\text{-}H6)}$ = 6.3 Hz; $J_{(H5\text{-}H4)}$ = 1.2 Hz). The observed conformation of the L-megosamine moiety in **9** is consistent with that found in the macrolide megalomycin.[12] As a result, the tertiary amine in **9** now points away from the aglycone, rather than towards it, which could have major implications for its biological activity.

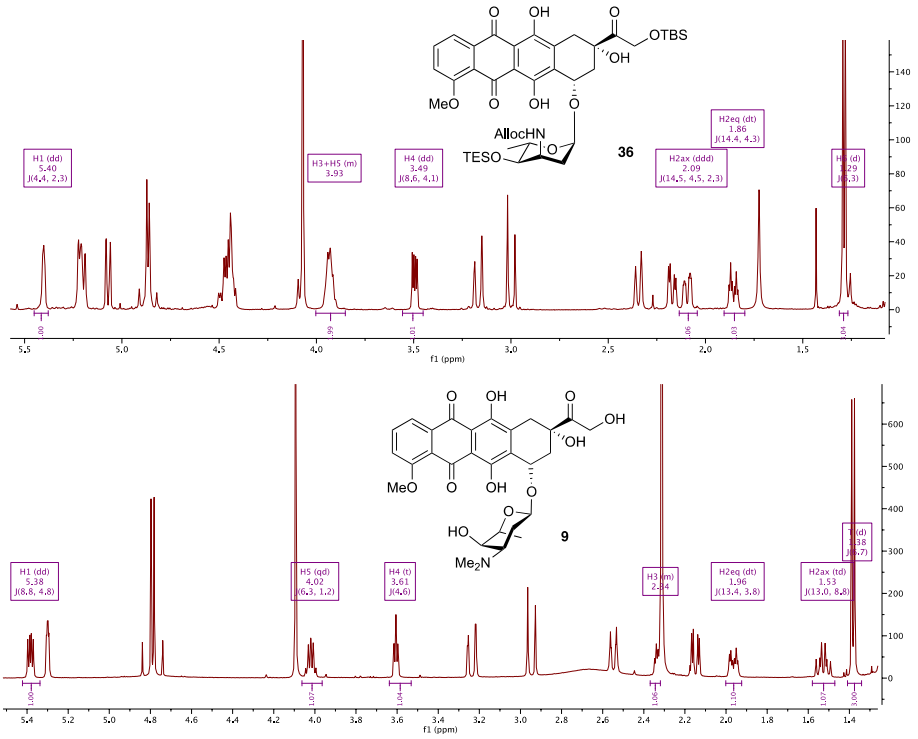
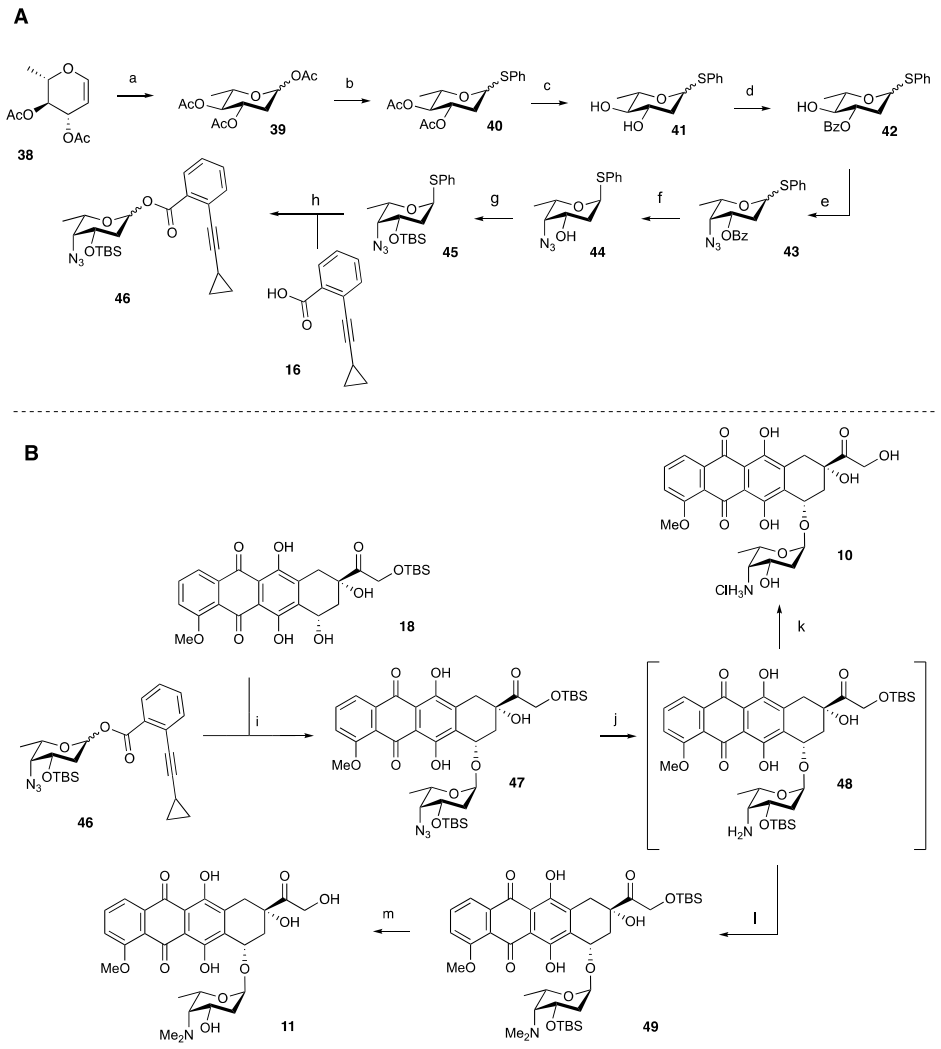


Figure 2. ^{1}H-NMR spectra of $^{1}C_{4}$-conformed **34a** and $^{4}C_{1}$-conformed **9**, zoomed in to the glycosidic protons and annotated with the chemical shift, peak splitting pattern and J-couplings.

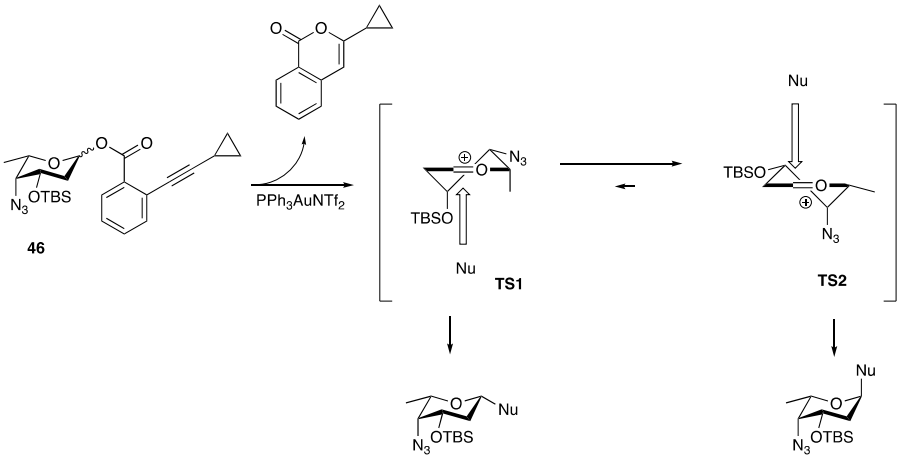
The synthesis of kedarosamine[13,14] donor **46** is depicted in Scheme 6A. Treatment of 3,4-di-*O*-acetyl-L-rhamnal **38** (Chapter 2) with catalytic PPh_3·HBr yielded 2-deoxyrhamnoside **39**, following the procedure reported by Oberthur *et al*.[15] Installation of an anomeric thiophenyl group was followed by Zemplén deacetylation to give diol **41**. A 3-benzoyl group was regioselectively introduced using catalytic dibutyltin dichloride[16] to yield **42**. Triflation of the C-4-OH followed by substitution with sodium azide yielded protected **43** in 68% over 2 steps. Crucial in the latter procedure was the (co-)evaporation at 0 °C at the end of the workup of the triflation reaction to prevent decomposition of the intermediate triflate. Debenzoylation was followed by installation of a TBS group on the 3-position to yield thioglycoside **45**. Subjection to hydrolysis of the anomeric group using the $AgNO_3$/lutidine system described in Chapter 4 afforded the corresponding hemiacetal. Final Steglich-esterification gave alkynylbenzoate **46**.



Scheme 6. Synthesis of 3,4-*iso*-doxorubicins **10** and **11**. *Reagents and conditions:* (a) AcOH, PPh_3·HBr, DCM, 51% (5:1 α:β); (b) PhSH, BF_3·Et_2O, DCM, quant.; (c) NaOMe, MeOH, 88%; (d) benzoyl chloride, Bu_2SnCl_2, DIPEA, THF, 84%; (e) *i.* triflic anhydride, pyr., 0 °C, *ii.* NaN_3, DMF, 68% over 2 steps; (f) NaOMe, MeOH, 86%; (g) TBS-Cl, imidazole, DMF, 94%; (h) *i.* $AgNO_3$, 2,6-lutidine, THF/H_2O; *ii.* EDCI·HCl, DMAP, DIPEA, DCM, 65% over 2 steps (1:3 α:β); (i) PPh_3AuNTf_2, DCM, 91% (>20:1 α:β); (j) PPh_3, THF, H_2O, 50 °C; (k) *i.* HF·pyr., pyr., 0 °C; *ii.* lyophilization from aq. HCl, 36% over 3 steps for **9**; (l) $NaBH(OAc_3)$, aq. CH_2O, EtOH, 43% over 2 steps; (m) HF·pyr., pyr., 0 °C, 72%.

Subjection of donor **46** and doxorubicinone acceptor **18** to catalytic gold(I) as depicted in Scheme 6B proceeded uneventfully to give the resulting glycoside **47** in excellent yield and stereoselectivity. As depicted in Scheme 7, the oxocarbenium ion that takes

up a $^3H_4$ conformation in TS2 is strongly favored over the alternative $^3H_4$ conformation, as it is able to put the large silyl ether in an equatorial position, with the incoming nucleophile suffering no steric hindrance. Additionally, the axial azide should be able to stabilize the oxocarbenium ion in this conformation. Conversely, β-face attack in TS1 is hindered by 1,3-diaxial hindrance induced by the TBS group and the 6-methyl substituent.



Scheme 7. Mechanistic rationale for the stereoselectivity found in the formation of **47**.

Staudinger reduction of azide **47** provided the corresponding amine **48**, after which global desilylation gave **10**. Reductive amination on amine **48** gave rise to dimethylamine **49**. Final desilylation yielded the envisaged regio-isomer of *N,N*-dimethyldoxorubicin (**2**), kedarosamino-doxorubicinone **11**.

Conclusions

Despite decades of use in the clinic and severe side effects, the structure-activity profile of doxorubicin remains poorly understood. The discovery of histone eviction as a cytotoxic property of anthracyclines comprises a new incentive for the synthesis of doxorubicin analogs. This Chapter describes the synthesis of stereo- and regio-isomers within the aminosugar moiety of doxorubicin using Yu's gold(I)-catalyzed glycosylation method. Additionally, the corresponding dimethylamines were prepared to be able to directly compare these compounds with doxorubicin (**1**) and *N,N*-dimethyldoxorubicin (**2**, Chapter 2). In all, the research described in this Chapter led to the synthesis of a set of known and unprecedented anthracyclines, specifically *N,N*-dimethyl-4-epidoxorubicin (**5**[17]), (*N,N*-dimethyl)-3-epidoxorubicin (**6**[18]) and (**7**), (*N,N*-dimethyl)-3,4-diepidoxorubicin (**8**[2,19]) and (**9**) and (*N,N*-dimethyl)-3',4'-isodoxorubicin (**10**[14]) and (**11**). The in literature obtained biological data on the known anthracyclines in this Chapter (**5**, **6**, **8** and **10**) is fragmented and incomplete. The now-available fully coherent set allows for side-by-side biological evaluation of these doxorubicin stereo- and regioisomers, and aid in understanding the structure-activity relationship of doxorubicin (**1**) and possibly assist in the identification of a better anti-cancer anthracycline.

Experimental procedures and characterization data

All reagents were of commercial grade and used as received. Traces of water from reagents were removed by co-evaporation with toluene in reactions that required anhydrous conditions. All moisture/oxygen sensitive reactions were performed under an argon atmosphere. DCM used in the glycosylation reactions was dried with flamedried 4Å molecular sieves before being used. Reactions were monitored by TLC analysis with detection by UV (254 nm) and where applicable by spraying with 20% sulfuric acid in EtOH or with a solution of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4{\cdot}2H_2O$ (10 g/L) in 10% sulfuric acid (aq.) followed by charring at ~150 °C. Flash column chromatography was performed on silica gel (40-63µm). ^1H and ^{13}C spectra were recorded on a Bruker AV 400 and Bruker AV 500 in $CDCl_3$, CD_3OD, pyridine-d5 or D_2O. Chemical shifts (δ) are given in ppm relative to tetramethylsilane (TMS) as internal standard (^1H NMR in $CDCl_3$) or the residual signal of the deuterated solvent. Coupling constants (J) are given in Hz. All ^{13}C spectra are proton decoupled. Column chromatography was carried out using silica gel (0.040-0.063 mm). Size-exclusion chromatography was carried out using Sephadex LH-20, using DCM:MeOH (1:1, v/v) as the eluent. Neutral silica was prepared by stirring regular silica gel in aqueous ammonia, followed by filtration, washing with water and heating at 150°C overnight. High-resolution mass spectrometry (HRMS) analysis was performed with a LTQ Orbitrap mass spectrometer (Thermo Finnigan), equipped with an electronspray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10 mL/min, capillary temperature 250 °C) with resolution R = 60000 at m/z 400 (mass range m/z = 150 – 2000) and dioctyl phthalate (m/z = 391.28428) as a "lock mass", or with a Synapt G2-Si (Waters), equipped with an electronspray ion source in positive mode (ESI-TOF), injection via NanoEquity system (Waters), with LeuEnk (m/z = 556.2771) as "lock mass". Eluents used: MeCN:H_2O (1:1 v/v) supplemented with 0.1% formic acid. The high-resolution mass spectrometers were calibrated prior to measurements with a calibration mixture (Thermo Finnigan).

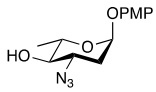
General procedure A: Oxidative hydrolysis of *p*-methoxyphenyl glycosides: To a solution of the glycoside in MeCN/H_2O (0.03 M, 1:1 v/v) were added NaOAc (10 eq) and $Ag(DPAH)_2{\cdot}H_2O$ (2.5 eq). The reaction mixture was stirred for 1h, diluted with sat. aq. $NaHCO_3$ and extracted thrice with DCM. Combined organics were dried over $MgSO_4$ and solvent was removed *in vacuo*. Column chromatography gave the crude hemiacetals.

General procedure B: Steglich esterification with *ortho*-cyclopropylbenzoic acid: To a solution of the hemiacetal in DCM (0.1 M) were added DIPEA (9 eq), DMAP (1 eq), EDCI·HCl (3.5 eq) and freshly saponified *o*-cyclopropylethynylbenzoic acid **16** (Chapter 2) (3 eq). After disappearance of the starting hemiacetal, the mixture was diluted with DCM and washed with sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography gave the corresponding anomeric benzoates.

General procedure C: Glycosylation of of alkynylbenzoate donors: To a solution of the alkynylbenzoate donor and 14-*O*-tert-butyldimethylsilyl-doxorubicinone **18** (Chapter 2) (1.5 eq) in DCM (0.05M), were added activated molecular sieves (4Å) and the mixture was stirred for 30 minutes. Subsequently, a freshly prepared 0.1M DCM solution of PPh_3AuNTf_2 (prepared by stirring 1:1 PPh_3AuCl and $AgNTf_2$ in DCM for 30 minutes) (0.1 eq) in DCM was added dropwise. After stirring 30 minutes, the mixture was filtered and concentrated *in vacuo*. Column chromatography gave the desired anthracyclines.

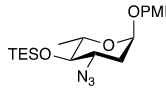
General procedure D: Global desilylation: A solution of the amine in pyridine (0.01-0.05 M) was cooled to 0 °C. HF·pyridine (70 wt% HF) was added and the reaction mixture was stirred for 1-5h at this temperature. Solid $NaHCO_3$ was added to quench and the mixture was stirred until cessation of effervescence. Salts were then filtered off and the filtrate was diluted with DCM (10 volumes), washed with H_2O, dried over Na_2SO_4 and concentrated *in vacuo*. Column chromatography gave the deprotected anthracyclines.

***p*-Methoxyphenyl-3-azido-2,3-dideoxy-α-L-rhamnopyranoside (13)**



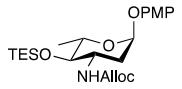
Acetate **11** (Chapter 2) (11.8 g, 3.72 mmol) was dissolved in MeOH (200 mL) and DCM (50 mL), NaOMe (400 mg, 37.4 mmol, 0.2 eq) was added and the reaction was stirred for 2 days. Dry ice was added to quench and the reaction mixture was concentrated in vacuo. Column chromatography (25:75 EtOAc:pentane) afforded the title compound as a white solid (10.38 g, 3.72 mmol, quant.). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.07 – 6.97 (m, 2H), 6.91 – 6.82 (m, 2H), 5.50 (d, J = 2.2 Hz, 1H), 3.99 (ddd, J = 12.1, 9.4, 4.9 Hz, 1H), 3.86 (dq, J = 9.4, 5.9 Hz, 1H), 3.81 (s, 3H), 3.25 (t, J = 9.4 Hz, 1H), 2.40 (ddd, J = 13.1, 4.9, 1.4 Hz, 1H), 2.24 (s, 1H), 1.89 (ddd, J = 13.2, 12.2, 3.5 Hz, 1H), 1.29 (d, J = 6.2 Hz, 3H).^{13}C NMR (101 MHz, Chloroform-d) δ 154.8, 150.4, 117.6, 114.6, 95.6, 76.0, 68.3, 60.3, 55.7, 35.2, 17.8. HRMS: [M + H]$^+$ calculated for $C_{13}H_{18}N_3O_4$: 280.1297; found 280.1292.

***p*-Methoxyphenyl-3-azido-2,3-dideoxy-4-*O*-triethylsilyl-α-L-rhamnopyranoside (14)**



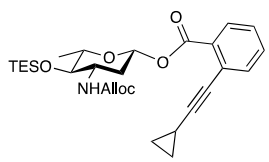
Alcohol **13** (370 mg, 1.32 mmol) was dissolved in DMF (2.23 mL) and pyridine (320 µL, 3.96 mmol, 3 eq) and cooled to 0 °C. TESOTf (0.51 mL, 2.38 mmol, 1.8 eq) was added and the reaction mixture was stirred for 1.5 h at the same temperature. Et_2O (80 mL) was added and the reaction mixture was washed with H_2O five times, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (5:95 EtOAc:pentane) afforded the title compound as a colourless oil (494 mg, 1.26 mmol, 95%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.04 – 6.98 (m, 2H), 6.89 – 6.82 (m, 2H), 5.47 (d, *J* = 2.3 Hz, 1H), 3.89 (ddd, *J* = 12.2, 9.2, 4.9 Hz, 1H), 3.85 – 3.81 (m, 1H), 3.80 (s, 3H), 3.19 (t, *J* = 9.2 Hz, 1H), 2.41 (ddd, *J* = 13.3, 4.9, 1.4 Hz, 1H), 1.88 (ddd, *J* = 13.2, 12.2, 3.5 Hz, 1H), 1.24 (d, *J* = 6.3 Hz, 3H), 1.03 (t, *J* = 7.9 Hz, 9H), 0.73 (qd, *J* = 7.9, 3.5 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8, 150.5, 117.6, 114.6, 95.5, 76.4, 69.2, 61.4, 55.6, 35.7, 18.2, 6.9, 5.2. HRMS: [M + Na]$^+$ calculated for $C_{19}H_{31}N_3O_4SiNa$ 416.1976; found 416.2671.

***p*-Methoxyphenyl-3-allyl-*N*-carbamate-2,3-dideoxy-4-*O*-triethylsilyl-α-L-rhamnopyranoside (15)**



To a solution of azide **14** (1.57 g, 4.00 mmol) in THF/H_2O (40 mL, 10:1 v/v) was added PPh_3 (3.15 g, 20.0 mmol, 5 eq) and the reaction mixture was stirred for 2 days at 50°C. Solvent was removed *in vacuo* and the residue was co-evaporated with toluene twice. The crude amine was dissolved in DCM (30 mL) and pyridine (1.0 mL, 12.9 mmol, 3.2 eq). Allyl chloroformate (0.64 mL, 24.0 mmol, 6 eq) was added at -20 °C and the resulting mixture was stirred for 2h at that temperature. It was then poured into H_2O and extracted with DCM thrice, combined organics were dried over $MgSO_4$ and solvent was removed *in vacuo*. Purification by column chromatography (0:100 – 5:95 EtOAc:pentane) afforded the title compound as a colourless oil (1.85 g, 4.0 mmol, quant.). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.08 – 6.93 (m, 2H), 6.89 – 6.76 (m, 2H), 5.94 (ddt, *J* = 16.5, 11.0, 5.7 Hz, 1H), 5.41 (d, *J* = 2.3 Hz, 1H), 5.33 (d, *J* = 16.5 Hz, 1H), 5.23 (dd, *J* = 10.4, 1.4 Hz, 1H), 4.59 (d, *J* = 5.7 Hz, 3H), 4.08 (dtd, *J* = 12.1, 9.2, 4.6 Hz, 1H), 3.83 (dq, *J* = 9.0, 6.3 Hz, 1H), 3.77 (s, 3H), 3.28 (t, *J* = 9.1 Hz, 1H), 2.32 (ddd, *J* = 13.3, 4.7, 1.5 Hz, 1H), 1.88 (t, *J* = 12.8 Hz, 1H), 1.21 (d, *J* = 6.3 Hz, 3H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.62 (q, *J* = 7.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.7, 154.7, 150.9, 133.0, 118.0, 117.7, 114.6, 95.8, 76.6, 69.7, 65.7, 55.8, 51.0, 36.7, 18.6, 7.1, 5.5. HRMS: [M + Na]$^+$ calculated for $C_{22}H_{24}NO_5Na$ 474.2282; found 474.2289.

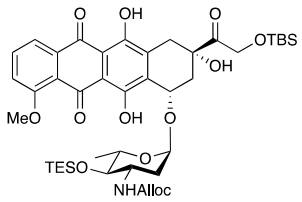
***o*-Cyclopropylethynylbenzoyl-3-*N*-allyloxycarbonyl-2,3-dideoxy-4-*O*-triethylsilyl-β-L-rhamnopyranoside (17)**



Glycoside **15** (903 mg, 2.00 mmol) was hydrolysed according to general procedure A. Column chromatography (30:70 – 50:50 EtOAc:pentane) afforded the hemiacetal. The hemiacetal in was esterified to according to general procedure B. Column chromatography (0:100 – 15:85 Et_2O:pentane) afforded the title compound as an off-white solid (498 mg, 0.97 mmol, 49%).^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.91 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.53 – 7.43 (m, 1H), 7.40 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.33 – 7.23 (m, 1H), 6.00 (dd, *J* = 9.6, 2.3 Hz, 1H), 5.93 (ddt, *J* = 16.5, 10.9, 5.7 Hz, 1H), 5.39 – 5.26 (m, 1H), 5.23 (d, *J* = 10.4 Hz, 1H), 4.73 (d, *J* = 8.8 Hz, 1H), 4.58 (d, *J* = 5.8 Hz, 2H), 3.76 (dtd, *J* = 12.1, 9.1, 4.7 Hz, 1H), 3.55 (dq, *J* = 8.6, 6.2 Hz, 1H), 3.33 – 3.22 (m, 1H), 2.40 (ddd, *J* = 12.7, 4.8, 2.4 Hz, 1H), 1.85 (q, *J* = 11.6 Hz, 1H), 1.51 (tt, *J* = 8.2, 6.1 Hz, 1H), 1.34 (d, *J* = 6.2 Hz, 3H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.93 – 0.84 (m, 4H), 0.63 (q, *J* = 8.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2, 155.5, 134.3, 134.1, 132.8, 132.1, 131.5, 131.1, 130.9, 127.4, 127.0, 125.2, 118.0,

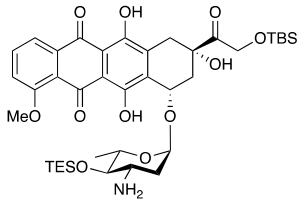
99.8, 92.6, 75.7, 75.0, 74.5, 65.8, 53.3, 36.6, 18.6, 9.1, 8.9, 7.0, 5.4, 0.8. HRMS: $[M + Na]^+$ calculated for $C_{28}H_{39}NO_6SiNa$ 536.2444; found 536.2437.

7-[3-*N*-allyloxycarbonyl-2,3-dideoxy-4-*O*-triethylsilyl-α-L-rhamnopyranoside]-14-*O*-*tert*-butyldimethylsilyldoxorubicinone (19)



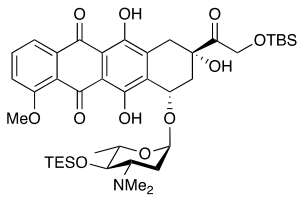
According to general procedure C, glycosyl donor **17** (411 mg, 0.800 mmol) was coupled to 14-O-*tert*-butyldimethylsilyl-doxorubicinone **18** (555 mg, 1.05 mmol 1.5 eq). Column chromatography (3:97 – 10:90 EtOAc:toluene) afforded the title compound as a red solid (545 mg, 0.64 mmol, 91%, 8:1 α:β). Spectral data for the α-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.96 (d, *J* = 2.6 Hz, 1H), 13.26 (d, *J* = 2.8 Hz, 1H), 8.03 (d, *J* = 6.4 Hz, 1H), 7.78 (td, *J* = 8.2, 2.2 Hz, 1H), 7.39 (d, *J* = 7.7 Hz, 1H), 5.99 – 5.78 (m, 1H), 5.47 – 5.40 (m, 1H), 5.27 (d, *J* = 15.3 Hz, 2H), 5.18 (d, *J* = 10.6 Hz, 1H), 5.03 – 4.86 (m, 2H), 4.57 (s, 1H), 4.08 (d, *J* = 2.1 Hz, 3H), 3.82 (d, *J* = 7.5 Hz, 1H), 3.63 (d, *J* = 9.6 Hz, 1H), 3.29 (s, 1H), 3.21 (d, *J* = 18.7 Hz, 1H), 2.98 (dd, *J* = 19.3, 2.8 Hz, 1H), 2.34 (d, *J* = 14.8 Hz, 1H), 2.16 (d, *J* = 15.1 Hz, 1H), 2.10 (d, *J* = 13.4 Hz, 1H), 1.81 (s, 1H), 1.30 (dd, *J* = 6.3, 2.1 Hz, 3H), 1.04 – 0.91 (m, 19H), 0.62 (qd, *J* = 7.9, 2.1 Hz, 6H), 0.14 (d, *J* = 2.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.9, 187.3, 186.9, 161.2, 156.6, 156.1, 135.8, 134.5, 134.0, 121.1, 111.6, 111.5, 90.0, 77.6, 77.3, 77.2, 76.9, 66.9, 36.0, 34.2, 18.8, 5.5. HRMS: $[M + Na]^+$ calculated for $C_{43}H_{61}NO_{13}Si_2Na$ 878.3574; found 878.3599.

7-[3-Amino-2,3-dideoxy-4-*O*-triethylsilyl-α-L-rhamnopyranoside]-14-*O*-*tert*-butyldimethylsilyldoxorubicinone (20)



To a solution of **19** (135 mg, 0.158 mmol) and 1,3-dimethylbarbituric acid (74 mg, 0.47 mmol, 3 eq) in DCM (15 mL) was portionwise added $Pd(PPh_3)_4$ (18.5 mg, 0.016 mmol, 0.1 eq). The reaction mixture was stirred overnight and solvent was removed *in vacuo*. The residue was submitted to column chromatography (3:97 – 15:85 acetone:toluene) to afford the title compound as a red solid (95 mg, 0.13 mmol, 78%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.93 (s, 1H), 8.00 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.76 (dd, *J* = 8.4, 7.8 Hz, 1H), 7.39 (dd, *J* = 8.6, 1.1 Hz, 1H), 5.43 (d, *J* = 3.8 Hz, 1H), 5.25 (dd, *J* = 4.1, 2.1 Hz, 1H), 5.03 – 4.82 (m, 2H), 4.73 (s, 1H), 4.08 (s, 3H), 3.73 (dq, *J* = 8.9, 6.2 Hz, 1H), 3.16 (dd, *J* = 19.0, 2.0 Hz, 1H), 3.06 (t, *J* = 8.9 Hz, 1H), 2.92 (d, *J* = 18.9 Hz, 1H), 2.87 (dt, *J* = 8.7, 4.1 Hz, 1H), 2.34 (dt, *J* = 14.7, 2.2 Hz, 1H), 2.18 – 2.05 (m, 1H), 1.95 (dd, *J* = 13.4, 4.4 Hz, 1H), 1.62 – 1.54 (m, 1H), 1.29 (d, *J* = 6.3 Hz, 3H), 1.05 – 0.93 (m, 18H), 0.69 (q, *J* = 8.1 Hz, 6H), 0.14 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.7, 187.1, 186.7, 161.1, 156.5, 155.9, 135.8, 135.6, 134.4, 134.1, 120.9, 119.9, 118.5, 111.5, 111.3, 100.7, 80.4, 70.0, 69.6, 66.8, 56.8, 50.3, 37.9, 35.8, 34.0, 26.0, 18.7, 18.4, 7.1, 5.7, -5.2. HRMS: $[M+H]^+$ calculated for $C_{39}H_{59}NO_{11}Si_2$ 772.3543; found 772.3568.

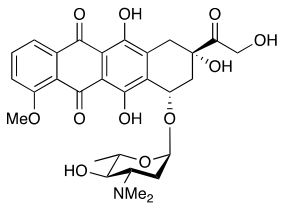
7-[3-Dimethylamino-2,3-dideoxy-4-*O*-triethylsilyl-α-L-rhamnopyranoside]-14-*O*-*tert*-butyldimethylsilyldoxorubicinone (21)



To a solution of **20** (97 mg, 0.13 mmol) in EtOH (10 mL) were added formaldehyde solution (aqueous 37% w/v, 0.31 mL, 3.9 mmol, 30 eq) and sodium trisacetoxyborohydride (52 mg, 0.24 mmol, 1.95 eq). After stirring for 1.5 h, the reaction mixture was partitioned between DCM and sat. aq. $NaHCO_3$ and extracted thrice with DCM. Combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (1:200 - 10:90 acetone:toluene) afforded the title compound as a red solid (77 mg, 96 µmol, 77%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.97 (s, 1H), 13.26 (s, 1H), 8.02 (d, *J* = 7.6 Hz, 1H), 7.78 (t, *J* = 7.9 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 5.50 (d, *J* = 3.9 Hz, 1H), 5.25 (d, *J* = 3.1 Hz, 1H), 5.06 – 4.85 (m, 2H), 4.79 (s, 1H), 4.09 (s, 3H), 3.82 – 3.68 (m, 1H), 3.32 – 3.12 (m, 2H), 3.00 (d, *J* = 18.8 Hz, 1H), 2.51 (d, *J* = 13.4 Hz, 1H), 2.37 (d, *J* = 14.7 Hz, 1H), 2.14 (d, *J* = 4.6 Hz, 6H), 1.89 – 1.79 (m, 1H), 1.60 (td, *J* = 12.9, 4.2 Hz, 1H), 1.31 (d, *J* = 6.1 Hz, 3H), 1.02

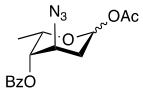
– 0.91 (m, 18H), 0.60 (qd, *J* = 7.6, 3.4 Hz, 6H), 0.14 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.8, 187.3, 186.8, 161.1, 156.6, 156.1, 135.8, 135.7, 134.6, 134.3, 121.1, 119.9, 118.5, 111.5, 111.4, 101.5, 73.6, 71.2, 69.8, 66.8, 61.8, 56.8, 40.7, 35.8, 34.0, 26.2, 26.0, 18.8, 18.7, 7.2, 5.6, -5.3. HRMS: $[M + H]^+$ calculated for $C_{41}H_{62}NO_{11}Si_2$: 800.3856; found 800.3888.

***N,N*-dimethyl-4'-*epi*-doxorubicin (5)**



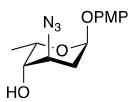
According to general procedure D, **21** (33 mg, 41 µmol) was subjected to HF·pyridine (70 wt% HF, 190 µL). Column chromatography on neutral silica (0:100 - 20:80 MeOH:DCM) afforded the title compound as a red solid (24 mg, 41 µmol, quant.). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 13.95 (s, 1H), 13.16 (s, 1H), 7.99 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.77 (dd, *J* = 8.5, 7.6 Hz, 1H), 7.39 (dd, *J* = 8.6, 1.1 Hz, 1H), 5.56 (d, *J* = 3.9 Hz, 1H), 5.29 (s, 1H), 5.26 (dd, *J* = 4.2, 2.1 Hz, 1H), 4.88 – 4.71 (m, 2H), 4.08 (s, 3H), 3.80 (dq, *J* = 9.0, 6.2 Hz, 1H), 3.23 – 3.12 (m, 2H), 2.90 (d, *J* = 18.7 Hz, 1H), 2.63 (ddd, *J* = 13.3, 9.9, 3.8 Hz, 1H), 2.38 (dt, *J* = 14.8, 2.2 Hz, 1H), 2.20 (s, 6H), 2.17 (dd, *J* = 14.7, 4.1 Hz, 1H), 1.84 (ddd, *J* = 13.2, 4.0, 1.3 Hz, 1H), 1.63 (td, *J* = 13.0, 4.2 Hz, 1H), 1.35 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.2, 187.2, 186.7, 161.1, 156.4, 155.8, 135.9, 135.5, 133.9, 133.9, 120.9, 120.0, 118.6, 111.6, 111.4, 101.5, 76.8, 71.5, 70.8, 69.8, 65.7, 61.9, 56.8, 40.0, 35.7, 34.0, 25.9, 18.4. HRMS: $[M+H]^+$ calculated for $C_{29}H_{35}NO_{11}$ 572.2126; found 572.2134.

Acetyl-3-*epi*-azido-4-*O*-benzoyl-3-deoxy-L-daunosamine (23)



A solution of **22** (Chapter 3)[8] (18.1 g, 45.0 mmol) in THF (360 mL) and 1M aq. HCl (360 mL) was stirred for 1 h at 50°C. It was then poured into sat. aq. $NaHCO_3$, extracted with DCM, dried over $MgSO_4$ and concentrated *in vacuo*. To a solution of the crude enal thus obtained in H_2O (64 mL) and THF (72 mL) were added acetic acid (9.6 mL, 167.7 mmol, 3.7 eq) and NaN_3 (5.12 g, 81.5 mmol, 1.8 eq). The reaction mixture was stirred for 2 days, poured into sat. aq. $NaHCO_3$, extracted with DCM, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was submitted to column chromatography (10:90 - 30:70 Et_2O:pentane) to yield the crude 3-azide hemiacetal. To a solution of the hemiacetal thus obtained in DCM (113 mL) and pyridine (34 mL) were added Ac_2O (34.0 mL, 360 mmol, 9.5 eq). The reaction mixture was stirred for 5 h, concentrated *in vacuo*, and partitioned between H_2O and EtOAc, washed with H_2O and brine, dried over $MgSO_4$ and concentrated *in vacuo* to obtain the product title product (7.92 g, 24.8 mmol, 55% over 3 steps, 1:5 α:β). Spectral data for the α-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.11 (dd, *J* = 8.4, 1.6 Hz, 2H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 6.25 (d, *J* = 4.3 Hz, 1H), 4.87 (s, 1H), 4.19 (d, *J* = 3.9 Hz, 1H), 2.37 – 2.27 (m, 2H), 2.19 – 2.16 (m, 1H), 2.15 (d, *J* = 1.3 Hz, 3H), 2.13 – 2.04 (m, 1H), 1.99 – 1.94 (m, 1H), 1.29 (d, *J* = 6.7 Hz, 3 H).^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.2, 165.8, 133.8, 130.0, 129.3, 128.7, 90.2, 69.8, 63.6, 54.0, 26.5, 21.3, 14.1. Spectral data for the β-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*): δ 8.11 (dd, *J* = 8.4, 1.6 Hz, 2H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 6.02 (dd, *J* = 9.5, 2.4 Hz, 1H), 4.89 (s, 1H), 4.29 (q, *J* = 6.6 Hz, 1H), 4.19 (d, *J* = 3.9 Hz, 1H), 2.37 – 2.27 (m, 2H), 2.19 – 2.16 (m, 1H), 2.15 (d, *J* = 1.3 Hz, 3H), 2.13 – 2.04 (m, 1H), 1.99 – 1.94 (m, 1H), 1.29 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 169.2. 165.8, 133.8, 130.0, 128.7, 90.6, 69.3, 57.7, 30.5, 21.3, 16.7. HRMS: $[M + Na]^+$ calculated for $C_{13}H_{15}N_3O_4Na$ 342.10604; found 342.10607.

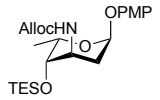
***p*-Methoxyphenyl-3-*epi*-azido-α-L-daunosamine (24)**



Anomeric acetate **23** (7.92 g, 24.8 mmol) and *p*-methoxyphenol (4.62 g, 37.2 mmol, 1.5 eq) were coevaporated with toluene. DCM (880 mL) and activated molecular sieves (4Å) were added and the reaction was stirred for 30 minutes at room temperature. $BF_3{\cdot}OEt_2$ (7.65 mL, 62 mmol, 2.5 eq) was added at -60 °C and the reaction mixture gradually allowed to warm up from -60 °C to -40 °C over 2.5h. The reaction mixture was poured into a saturated aqueous solution of $NaHCO_3$, extracted with DCM, washed twice with NaOH, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in MeOH (42 ml), to which NaOMe (284 mg, 5.0 mmol, 0.2 eq) was added after which the reaction mixture was stirred for 4 days. Dry ice was added and the reaction mixture was concentrated *in vacuo*. Column chromatography (8:92 – 40:60 EtOAc:pentane) afforded the title compound as a white solid (4.38 g, 17.3 mmol, 77%, 10:1 α:β). Spectral data for

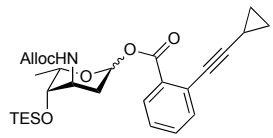
the α-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.13 – 6.94 (m, 2H), 6.94 – 6.73 (m, 2H), 5.46 (dd, *J* = 4.3, 1.4 Hz, 1H), 4.43 (qd, *J* = 6.7, 1.4 Hz, 1H), 4.00 (dt, *J* = 4.2, 3.1 Hz, 1H), 3.80 (s, 3H), 3.43 (s, 1H), 2.35 (dt, *J* = 15.3, 4.4 Hz, 1H), 2.26 – 2.05 (m, 2H), 1.22 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8, 151.0, 117.8, 114.6, 95.3, 69.0, 62.7, 57.1, 55.7, 29.7, 27.0, 16.3. HRMS: $[M + H]^+$ calculated for $C_{13}H_{18}N_3O_4$ 280.1297; found 280.1292.

***p*-Methoxyphenyl-3-*epi*-*N*-allyloxycarbonyl-4-*O*-triethylsilyl-α-L-daunosamine (26)**



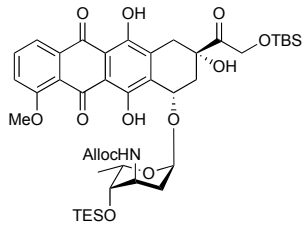
To a solution of **25** (1.22 mg, 4.38 mmol) in DMF (7.4 mL) and pyridine (1.06 mL, 13.1 mmol, 3 eq) was added TESOTf (1.08 mL, 1.8 mmol, 1.8 eq) at 0°C and the reaction mixture was stirred for 1 hour. It was subsequently poured into EtOAc, washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo.* The residue was dissolved in THF/H_2O (165 mL, 10:1 v/v), PPh_3 (2.30 g, 8.76 mmol, 2 eq) was added and the reaction mixture was stirred for 3 days after which it was concentrated *in vacuo*. The amine thus obtained was co-evaporated with toluene thrice and dissolved in DCM (31.4 mL) and pyridine (1.1 mL, 14 mmol, 3.2 eq). Allyl choroformate (0.70 mL, 6.6 mmol, 1.5 eq) was added at -25 °C and the reaction mixture was stirred at that temperature for 1h. The mixture was left to warm to room temperature and diluted with DCM, washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo.* Purification by column chromatography (2:98:1 – 40:60:1 Et_2O:pentane:Et_3N) afforded the title compound as a colourless oil (1.98 g, 4.38 mmol, quant. over 3 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.07 – 6.98 (m, 2H), 6.91 – 6.77 (m, 2H), 6.29 (d, *J* = 7.8 Hz, 1H), 5.96 (ddt, *J* = 17.2, 10.3, 5.6 Hz, 1H), 5.48 (d, *J* = 3.7 Hz, 1H), 5.41 – 5.16 (m, 2H), 4.72 – 4.50 (m, 2H), 4.26 – 4.13 (m, 1H), 3.90 (ddt, *J* = 7.9, 5.4, 2.7 Hz, 1H), 3.78 (s, 3H), 3.53 (d, *J* = 3.4 Hz, 1H), 2.52 – 2.32 (m, 1H), 1.79 (ddt, *J* = 14.4, 2.4, 1.2 Hz, 1H), 1.16 (d, *J* = 6.5 Hz, 3H), 1.06 – 0.95 (m, 9H), 0.80 – 0.64 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7, 155.1, 150.7, 133.1, 118.0, 117.9, 114.7, 97.6, 69.4, 65.7, 63.4, 55.8, 49.1, 27.9, 17.2, 7.0, 4.9. HRMS: $[M + Na]^+$ calculated for $C_{19}H_{31}N_3O_4SiNa$ 474.2282; found 474.2289.

***o*-Cyclopropylethynylbenzoyl-3-*epi*-*N*-allyloxycarbonyl-4-*O*-triethylsilyl-L-daunosamine (27)**



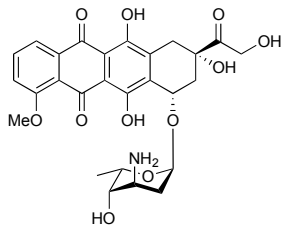
Glycoside **26** (990 mg, 2.19 mmol) was hydrolyzed according to general procedure A. The hemiacetal thus obtained was esterified according to general procedure B. Column chromatography (0:100 – 15:85 Et_2O) in pentane afforded the title compound as a pale-yellow oil (879 mg, 1.71 mmol, 79%, 3:1 α:β). Spectral data for the α-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.96 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 1H, NH), 7.47 (dt, *J* = 7.5, 1.9 Hz, 1H), 7.44 – 7.38 (m, 1H), 7.34 – 7.27 (m, 1H), 6.09 (dd, *J* = 9.2, 2.5 Hz, 1H), 5.93 (ddd, *J* = 16.2, 10.8, 5.4 Hz, 1H), 5.37 – 5.22 (m, 2H), 4.59 (s, 2H), 4.00 (dt, *J* = 6.5, 2.9 Hz, 2H), 3.57 (s, 1H), 2.42 – 2.34 (m, 1H), 1.88 – 1.78 (m, 1H), 1.31 – 1.27 (m, 3H), 1.27 – 1.23 (m, 1H), 0.98 (t, *J* = 7.9 Hz, 9H), 0.91 – 0.88 (m, 4H), 0.73 – 0.65 (m, 8H). ^{13}C NMR (100 MHz, Chloroform-*d*): δ 164.7, 155.6, 134.9, 134.3, 132.1, 130.8, 127.2, 99.9, 91.8, 74.6, 71.5, 69.3, 65.9, 50.7, 30.6, 17.0, 9.0, 7.1, 4.85, 0.8. HRMS: $[M + Na]^+$ calculated for $C_{28}H_{39}NO_6SiNa$ 536.24389; found 536.24362.

7-[3-*epi*-*N*-allyloxycarbonyl-4-*O*-triethylsilyl-α-L-daunosamino]-14-*O*-tert-butyldimethylsilyldoxorubicinone (28)



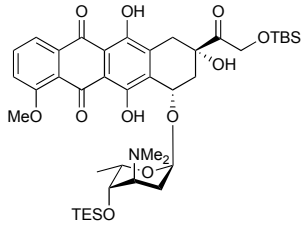
According to general procedure C glycosyl donor **27** (384 mg, 0.769 mmol) was coupled to 14-O-*tert*-butyldimethylsilyl-doxorubicinone **18** (593 mg, 0.2 mmol 1.5 eq). Column chromatography (2:98 – 10:90 acetone:toluene) and size-exclusion chromatography (Sephadex LH-20, 1:1 DCM:MeOH v/v) afforded the title compound as a red solid (368 mg, 0.43 mmol, 57%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.95 (s, 1H), 13.24 (s, 1H), 7.99 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.76 (t, *J* = 8.1 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 6.71 (d, *J* = 7.7 Hz, 1H), 6.00 – 5.80 (m, 1H), 5.50 (d, *J* = 3.7 Hz, 1H), 5.40 – 5.01 (m, 3H), 4.74 (s, 2H), 4.51 (dt, *J* = 5.5, 1.5 Hz, 2H), 4.20 – 4.13 (m, 1H), 4.11 (s, 1H), 4.08 (s, 3H), 3.81 – 3.71 (m, 1H), 3.49 (d, *J* = 3.6 Hz, 1H), 3.19 (d, *J* = 18.8 Hz, 1H), 3.02 (d, *J* = 18.8 Hz, 1H), 2.39 – 2.09 (m, 3H), 1.21 (d, *J* = 6.5 Hz, 3H), 0.96 (d, *J* = 24.0 Hz, 19H), 0.70 (q, *J* = 7.7 Hz, 6H), 0.15 (d, *J* = 1.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.9, 187.1, 186.7, 161.1, 156.8, 155.8, 135.8, 135.6, 135.1, 133.7, 133.3, 121.0, 119.8, 118.5, 117.3, 111.5, 111.2, 99.4, 76.1, 69.5, 67.0, 66.9, 65.3, 63.6, 56.8, 48.7, 35.2, 33.5, 27.4, 25.9, 18.5, 17.2, 7.1, 4.9, -5.3. HRMS: $[M + Na]^+$ calculated for $C_{43}H_{61}NO_{13}Si_2Na$ 878.35740; found 878.35817.

3'-*epi*-Doxorubicin (6)



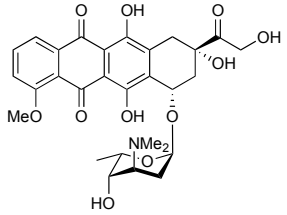
To a solution of **28** (46 mg, 54 µmol) in DCM (5 mL) were added 1,3-dimethylbarbituric acid (25 mg, 0.16 mmol, 3 eq) and $Pd(PPh_3)_4$ (27 mg, 5.4 µmol, 0.05 eq). The reaction mixture was stirred for 1.5 h after which solvent was removed *in vacuo*. The residue was submitted to column chromatography (0:100 – 10:90 acetone:toluene) to afford the crude amine **29**. The crude amine was desilylated using HF·pyridine (70 wt% HF, 0.2 mL) according to general procedure D. Column chromatography on neutral silica (0:100 - 50:50 MeOH:DCM) afforded the title compound as a red solid (18 mg, 33 µmol, 62% over 2 steps). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 13.93 (s, 1H), 8.04 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.79 (dd, *J* = 8.5, 7.7 Hz, 1H), 7.39 (dd, *J* = 8.6, 1.1 Hz, 1H), 5.46 – 5.37 (m, 1H), 5.25 (dd, *J* = 3.7, 2.4 Hz, 1H), 4.79 (s, 2H), 4.59 – 4.42 (m, 1H), 4.09 (s, 3H), 3.79 – 3.66 (m, 1H), 3.08 (d, *J* = 18.9 Hz, 1H), 2.39 (dt, *J* = 14.7, 2.2 Hz, 1H), 2.21 – 2.04 (m, 2H), 1.94 – 1.80 (m, 2H), 1.46 (d, *J* = 12.1 Hz, 2H), 1.29 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.8, 187.2, 186.8, 161.2, 156.3, 156.0, 135.8, 135.7, 134.6, 134.0, 121.1, 119.9, 118.5, 111.6, 111.3, 100.0, 76.4, 72.0, 68.3, 65.7, 62.9, 48.7, 35.5, 34.1, 31.2, 16.4. HRMS: $[M+H^+]$ calculated for $C_{27}H_{30}NO_{11}$: 544.1813; found 544.1812.

7-[3-*epi*-Dimethylamino-4-*O*-triethylsilyl-α-L-daunosamine]-14-*O*-tert-butyldimethylsilyldoxorubicinone (30)



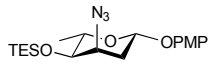
To a solution of **28** (34 mg, 40 µmol) in DCM (4.0 mL) was added 1,3-dimethylbarbituric acid (19 mg, 119 µmol, 3 eq). $Pd(PPh_3)_4$ (5 mg, 4 µmol, 0.1 eq) was added and the reaction mixture was stirred for 1h, after which it was concentrated *in vacuo*. The residue was submitted to column chromatography (0:100 – 15:85 acetone:toluene) to give the crude amine. To a solution of this amine in EtOH (2.5 mL) was added formaldehyde (aqueous 37% w/v solution, 0.1 mL, mmol, 30 eq) and sodium trisacetoxy borohydride (14 mg, 66 µmol, 1.95 eq). The reaction mixture was stirred for 2h and partitioned between DCM and sat. aq. $NaHCO_3$. The aqueous layer was extracted with DCM, combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (0:100 – 10:90 acetone in toluene) afforded the title compound as a red solid (23 mg, 29 µmol, 72%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.85 (s, 1H), 13.31 (s, 1H), 8.02 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.76 (dd, *J* = 8.5, 7.7 Hz, 1H), 7.38 (dd, *J* = 8.6, 1.2 Hz, 1H), 5.34 (d, *J* = 3.7 Hz, 1H), 5.18 (dd, *J* = 3.6, 2.3 Hz, 1H), 5.00 – 4.90 (m, 2H), 4.24 (h, *J* = 5.7 Hz, 1H), 4.08 (s, 3H), 3.77 – 3.71 (m, 1H), 3.44 – 3.26 (m, 1H), 3.22 – 2.98 (m, 2H), 2.39 – 2.26 (m, 1H), 2.15 (s, 6H), 2.12 – 1.98 (m, 3H), 1.82 – 1.70 (m, 1H), 1.21 (d, *J* = 6.5 Hz, 3H), 1.03 – 0.93 (m, 19H), 0.71 – 0.56 (m, 6H), 0.14 (d, *J* = 3.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.0, 187.2, 186.8, 161.1, 156.5, 156.3, 135.8, 135.7, 135.4, 134.7, 121.2, 119.8, 118.4, 111.3, 111.1, 99.9, 76.8, 68.9, 67.7, 66.8, 64.7, 64.0, 56.8, 44.0, 35.7, 34.0, 26.0, 25.6, 18.8, 17.5, 7.1, 5.1, -5.1, -5.3. HRMS: $[M+H]^+$ calculated for $C_{41}H_{62}NO_{11}Si_2$ 800.3856; found 800.3880.

***N,N*-dimethyl-3'-epidoxorubicin (7)**



According to general procedure D, **30** (19 mg, 24 µmol) was desilylated using HF·pyridine (70 wt% HF, 0.2 mL). Column chromatography on neutral silica (0:100 - 20:80 MeOH:DCM) afforded the title compound as a red solid (9.0 mg, 16 µmol, 66%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 13.95 (s, 1H), 13.27 (s, 1H), 8.04 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.80 (dd, *J* = 8.5, 7.7 Hz, 1H), 7.41 (dd, *J* = 8.6, 1.1 Hz, 1H), 5.36 (dd, *J* = 5.5, 3.9 Hz, 1H), 5.28 (dd, *J* = 3.7, 2.3 Hz, 1H), 4.80 (s, 2H), 4.38 (qd, *J* = 6.8, 3.4 Hz, 1H), 4.10 (s, 3H), 3.74 (dd, *J* = 6.6, 3.4 Hz, 1H), 3.23 (dd, *J* = 18.9, 2.0 Hz, 1H), 3.04 (d, *J* = 18.8 Hz, 1H), 2.52 – 2.41 (m, 2H), 2.23 (s, 6H), 2.11 (dd, *J* = 14.7, 3.8 Hz, 1H), 1.98 (dt, *J* = 14.0, 3.8 Hz, 1H), 1.60 (ddd, *J* = 13.7, 8.0, 5.5 Hz, 1H), 1.32 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.0, 187.2, 186.8, 161.1, 156.3, 156.0, 135.7, 134.3, 134.3, 121.0, 119.9, 111.5, 111.3, 99.7, 77.4, 77.1, 76.9, 76.4, 76.4, 68.5, 68.2, 66.9, 65.7, 62.6, 56.8, 35.6, 34.0, 26.4, 26.4, 15.1. HRMS: $[M+H]^+$ calculated $C_{29}H_{35}NO_{11}$ for 572.2126; found 572.2131.

***p*-Methoxyphenyl-3-azido-4-*O*-triethylsilyl-2,3,6-trideoxy-β-L-ribohexapyranoside (32)**



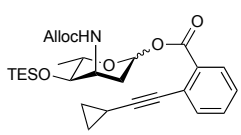
To a solution of **31** (Chapter 2) (2.26 g, 7.03 mmol) in MeOH (120 ml) was added sodium methoxide (76 mg, 1.41 mmol, 0.2 eq). After stirring for two days the reaction mixture was quenched by addition of dry ice. Solvent was removed in vacuo and coevaporated thrice with toluene. The residue was purified by column chromatography (10:90 – 50:50 Et_2O:pentane) to afford the alcohol as a pale-yellow oil (1.96 mg, 7.03 mmol, quant.). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.03 – 6.89 (m, 2H), 6.90 – 6.76 (m, 2H), 5.27 (dd, *J* = 8.9, 2.3 Hz, 1H), 4.11 (q, *J* = 3.7 Hz, 1H), 3.80 (dt, *J* = 8.7, 6.3 Hz, 1H), 3.76 (s, 3H), 3.48 (td, *J* = 8.3, 3.6 Hz, 1H), 2.28 (ddd, *J* = 13.8, 4.2, 2.3 Hz, 1H), 2.13 – 1.99 (m, 1H), 1.32 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.0, 151.1, 117.7, 114.6, 96.3, 72.4, 70.8, 60.7, 55.7, 35.1, 18.2. HRMS: $[M+Na]^+$ calculated for $C_{13}H_{17}N_3O_4Na$ 302.1111; found 302.1118.

To a solution of the above alcohol (1.12 g, 4.00 mmol) in pyridine (20 mL) was added TESOTf (1.29 mL, 1.59 g, 6.00 mmol, 1.5 eq). The reaction mixture was stirred for 30 minutes and then diluted with DCM, washed twice with 1M HCl, sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (0:100 – 7:93 Et_2O:pentane) afforded the title compound as a colorless oil (1.57 g, 4.0 mmol quant.). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.97 – 6.90 (m, 2H), 6.86 – 6.75 (m, 2H), 5.25 (dd, *J* = 9.0, 2.3 Hz, 1H), 3.98 (q, *J* = 3.5 Hz, 1H), 3.96 – 3.87 (m, 1H), 3.77 (s, 3H), 3.62 (dd, *J* = 8.7, 3.3 Hz, 1H), 2.17 (ddd, *J* = 13.6, 4.0, 2.3 Hz, 1H), 1.96 (ddd, *J* = 13.6, 9.0, 3.4 Hz, 1H), 1.28 (d, *J* = 6.3 Hz, 3H), 1.00 (t, *J* = 7.9 Hz, 9H), 0.68 (qd, *J* = 8.3, 7.9, 1.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.0, 151.2, 117.8, 114.6, 96.5, 74.8, 70.8, 60.8, 55.8, 35.8, 18.5, 7.0, 5.0. HRMS: $[M+Na]^+$ calculated for $C_{19}H_{31}N_3O_4SiNa$ 416.1976; found 416.1983.

***p*-Methoxyphenyl-3-*N*-allyloxycarbonyl-4-*O*-triethylsilyl-2,3,6-trideoxy-3-azido-β-L-ribohexapyranoside (34)**

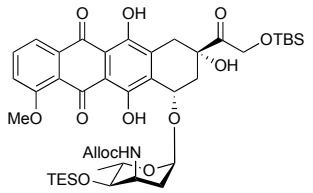
To a solution of **33** (1.57 mg, 4.00 mmol) in THF/H_2O (40 ml, 10:1 v/v) was added PPh_3 (3.15 g, 2.00 mmol, 2 eq) and the reaction mixture was stirred overnight at 50°C. Solvent was removed *in vacuo* and the residue was co-evaporated with toluene twice. The crude amine was dissolved in DCM (30 ml) and pyridine (1 mL) to which allyl chloroformate (0.64 ml, 0.72 g, 6 eq) was added at -20°C. This mixture was stirred for 1 hour at this temperature. It was then poured into H_2O and extracted with DCM thrice, organic layers dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (1:200 Et_3N:pentane) afforded the title compound as a colorless oil (1.81 mg, 4.00 mmol quant.). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.03 – 6.91 (m, 2H), 6.87 – 6.70 (m, 2H), 5.93 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H), 5.43 – 5.25 (m, 2H), 5.22 (dq, *J* = 10.4, 1.4 Hz, 1H), 5.04 (s, 1H), 4.65 – 4.45 (m, 2H), 4.11 (q, *J* = 4.9, 4.2 Hz, 1H), 3.77 (s, 4H), 3.63 (dd, *J* = 6.7, 4.0 Hz, 1H), 2.51 (dd, *J* = 14.0, 6.3 Hz, 1H), 1.90 (ddd, *J* = 13.5, 7.0, 3.7 Hz, 1H), 1.28 (d, *J* = 6.5 Hz, 3H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.63 (q, *J* = 7.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.3, 154.8, 151.4, 132.9, 117.9, 117.6, 114.6, 97.0, 72.6, 71.9, 65.7, 55.8, 48.4, 19.2, 6.9, 5.0. HRMS: $[M+Na]^+$ calculated for $C_{23}H_{37}NO_6SiNa$ 474.2282; found 474.2290.

***o*-Cyclopropylethynylbenzoyl-3-*N*-allyloxycarbonyl-4-*O*-triethylsilyl-2,3,6-trideoxy-L-ribohexapyranoside (35)**



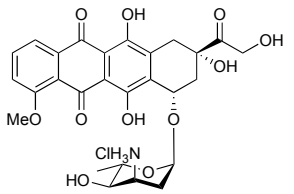
Glycoside **34** (1.71 g, 3.80 mmol) was hydrolyzed according to general procedure A. Column chromatography (90:10 EtOAc:pentane) afforded the hemiacetal. The resulting hemiacetal was esterified according to general procedure B. Column chromatography (0:100 -10:90 Et_2O:pentane) afforded the title compound as a pale yellow oil (1.11 g, 2.20 mmol, 57% over 2 steps, 1:3 α:β). Spectral data for the β-anomer: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.91 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.47 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.41 (tt, *J* = 7.7, 1.2 Hz, 1H), 7.33 – 7.27 (m, 1H), 6.27 (dd, *J* = 6.6, 2.8 Hz, 1H), 5.93 (dddd, *J* = 18.0, 10.5, 6.1, 5.2 Hz, 1H), 5.32 (dq, *J* = 17.2, 1.3 Hz, 1H), 5.23 (dq, *J* = 10.4, 1.3 Hz, 1H), 5.06 (s, 1H), 4.59 (q, *J* = 6.8, 6.2 Hz, 2H), 4.15 (tq, *J* = 6.6, 3.7 Hz, 1H), 3.91 (p, *J* = 6.5 Hz, 1H), 3.67 (dd, *J* = 6.1, 3.9 Hz, 1H), 2.55 – 2.39 (m, 1H), 1.93 (ddd, *J* = 13.5, 6.6, 3.8 Hz, 1H), 1.53 (tt, *J* = 8.1, 5.6 Hz, 1H), 1.32 (d, *J* = 6.6 Hz, 3H), 0.97 (dd, *J* = 8.3, 7.5 Hz, 9H), 0.92 – 0.83 (m, 4H), 0.63 (q, *J* = 7.8 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.6, 156.2, 134.4, 132.9, 131.9, 131.2, 130.6, 127.1, 125.2, 117.9, 99.8, 92.1, 74.6, 73.6, 71.5, 65.8, 47.6, 32.2, 19.3, 9.0, 6.9, 5.0, 0.8. HRMS: $[M+Na]^+$ calculated for $C_{28}H_{39}NO_6SiNa$ 536.2434; found 536.2450.

7-[3-Allyl-*N*-allyloxycarbonyl-4-*O*-triethylsilyl-2,3,6-trideoxy-L-ribohexapyranoside]-14-*O*-tert-butyldimethylsilyldoxorubicinone (36)



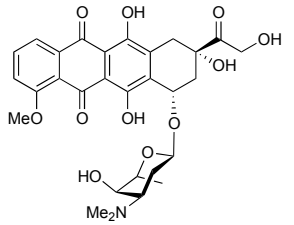
According to general procedure C, glycosyl donor **35** (128 mg, 0.240 mmol) was coupled to 14-O-*tert*-butyldimethylsilyldoxorubicinone **18** (198 mg, 0.37 mmol, 1.5 eq). Column chromatography (0:100 – 5:95 EtOAc:pentane - 1:99 - 3:97 acetone:toluene) gave the title compound as a red solid (103 mg, 0.120 mmol, 50%, 1.5:1 α:β). Spectral data for the α-anomer: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 13.92 (s, 1H), 13.22 (s, 1H), 7.98 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.74 (t, *J* = 8.1 Hz, 1H), 7.37 (d, *J* = 8.5 Hz, 1H), 5.82 (ddt, *J* = 17.3, 10.6, 5.4 Hz, 1H), 5.71 (d, *J* = 6.7 Hz, 1H), 5.40 (dd, *J* = 4.4, 2.3 Hz, 1H), 5.26 – 5.17 (m, 2H), 5.07 (dq, *J* = 10.5, 1.5 Hz, 1H), 4.95 – 4.78 (m, 2H), 4.54 – 4.37 (m, 3H), 4.07 (s, 3H), 3.93 (dq, *J* = 12.5, 6.5 Hz, 2H), 3.49 (dd, *J* = 8.6, 4.1 Hz, 1H), 3.17 (dd, *J* = 18.9, 1.8 Hz, 1H), 3.00 (d, *J* = 18.8 Hz, 1H), 2.34 (dt, *J* = 14.7, 2.1 Hz, 1H), 2.17 (dd, *J* = 14.7, 4.2 Hz, 1H), 2.09 (ddd, *J* = 14.5, 4.5, 2.3 Hz, 1H), 1.86 (dt, *J* = 14.4, 4.3 Hz, 1H), 1.29 (d, *J* = 6.3 Hz, 3H), 0.99 – 0.93 (m, 18H), 0.71 – 0.59 (m, 6H), 0.15 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.3, 186.9, 186.6, 161.0, 156.4, 156.3, 155.7, 135.6, 135.5, 134.5, 134.0, 133.1, 120.9, 119.7, 118.4, 116.9, 111.4, 111.2, 98.9, 72.5, 66.8, 66.4, 65.1, 56.7, 48.4, 35.6, 33.7, 33.4, 25.8, 18.5, 18.1, 6.8, 4.8, -5.5. HRMS: [M+Na$^+$] calculated for $C_{43}H_{61}NO_{13}Si_2Na$ 878.3574; found 878.3602.

3'-4'-Di-*epi*-dimethyldoxorubicin hydrochloride (8)



To a solution of **36** (45mg, 53 µmol) in DCM (5 mL) were added 1,3-dimethylbarbituric acid (25 mg, 0.16 mmol, 3 eq) and $Pd(PPh_3)_4$ (6.0 mg, 5.3 mmol, 0.1 eq). The reaction mixture was stirred overnight and solvent was removed in vacuo. The residue was submitted to column chromatography (1:99 – 15:85 acetone in toluene) to give the crude amine **37**. The crude amine thus obtained was desilylated according to general procedure D using HF·pyridine (70 wt% HF, 0.2 mL). Column chromatography on neutral silica (0:100 - 50:50 MeOH:DCM) and lyophilization from aqueous 10 µM HCl (1 mL/µmol, 2 eq) afforded the title compound as a dark red solid (17 mg, 29 µmol, 54% over 2 steps). ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.98 (s, 1H), 13.22 (s, 1H), 7.92 (q, *J* = 4.4, 3.8 Hz, 2H), 7.80 – 7.55 (m, 4H), 6.29 (s, 1H), 6.18 (d, *J* = 4.8 Hz, 1H), 5.30 (d, *J* = 3.3 Hz, 1H), 5.04 – 4.89 (m, 2H), 4.73 – 4.43 (m, 2H), 3.99 (s, 3H), 3.98 – 3.91 (m, 1H), 3.46 (dt, *J* = 9.3, 4.5 Hz, 3H), 3.17 (d, *J* = 18.8 Hz, 1H), 3.00 (d, *J* = 18.8 Hz, 1H), 2.24 (d, *J* = 14.8 Hz, 1H), 2.11 – 1.81 (m, 3H), 1.28 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO) δ 214.0, 187.2, 187.1, 161.4, 156.1, 155.1, 136.9, 135.3, 135.1, 134.6, 120.5, 120.4, 119.6, 111.4, 111.3, 98.7, 75.7, 68.9, 68.6, 65.0, 64.4, 57.2, 49.7, 40.4, 35.6, 32.1, 31.7, 18.0. HRMS: [M+H$^+$] calculated for $C_{27}H_{31}NO_{11}$:544.1813; found 544.1814.

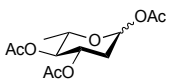
3'-4'-Di-*epi*-dimethyldoxorubicin (9)



To a solution of **36** (73 mg, 85 µmol) in DCM (6 mL) was added 1,3-dimethylbarbituric acid (40 mg, 0.26 mmol, 3 eq). $Pd(PPh_3)_4$ (9.0 mg, 8.5 µmol, 0.1 eq) was added and the reaction mixture was stirred overnight. After concentrating *in vacuo,* the residue was submitted to silica gel column chromatography (0:100 - 15:85 acetone in toluene) to give the crude amine **37**. To a solution of the crude amine in EtOH (4 mL) was added formaldehyde (aqueous 37% w/v solution, 0.13 mL) and sodium trisacetoxyborohydride (22.5 mg, 106 µmol, 1.95 eq). The reaction mixture was stirred for 2h, partitioned between DCM and sat. aq. $NaHCO_3$ and the aqueous layer was extracted thrice with DCM. Combined organics were dried over Na_2SO_4 and concentrated *in vacuo*, followed by purification through column chromatography (0:100 – 20:80 acetone in toluene) to give the crude dimethylamine. This was then desilylated using HF·pyridine (70 wt% HF, 0.3 mL) according to general procedure D. Column chromatography on neutral silica (0:100 - 7:93 MeOH:DCM) afforded the title compound as a red solid (17 mg, 30 µmol, 35% over 3 steps). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 13.99 (s, 1H), 13.22 (s, 1H), 8.03 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.79 (dd, *J* = 8.5, 7.7 Hz, 1H), 7.40 (dd, *J* = 8.6, 1.1 Hz, 1H), 5.38 (dd, *J* = 8.8, 4.8 Hz, 1H), 5.30 (dd, *J* = 4.1, 2.1 Hz, 1H), 4.85 – 4.71 (m, 2H), 4.09 (s, 3H), 4.02

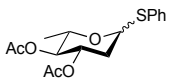
(dd, *J* = 6.8, 5.3 Hz, 1H), 3.64 – 3.53 (m, 1H), 3.24 (dd, *J* = 18.8, 2.1 Hz, 1H), 2.95 (d, *J* = 18.7 Hz, 1H), 2.55 (dt, *J* = 14.6, 2.2 Hz, 1H), 2.37 – 2.31 (m, 6H), 2.31 (s, 6H), 2.15 (dd, *J* = 14.7, 4.1 Hz, 1H), 2.00 – 1.91 (m, 1H), 1.53 (td, *J* = 13.0, 8.8 Hz, 1H), 1.38 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.9, 187.3, 186.7, 161.2, 156.5, 156.0, 135.9, 135.7, 134.4, 133.9, 121.0, 120.0, 118.5, 111.6, 111.4, 100.3, 76.6, 71.4, 69.0, 68.3, 65.8, 60.1, 56.8, 43.0, 36.0, 33.9, 29.0, 18.7. HRMS: [M+H$^+$] calculated $C_{29}H_{35}NO_{11}$ 572.2126; found 572.2131. ^{13}C-GATED NMR (Chloroform-*d*, 126 MHz) δ 100.31 ($J_{C1', H1'}$ = 169 Hz, C-1).

1,3,4-Tri-*O*-acetyl-2-deoxy-L-rhamnopyranoside (39)[15]



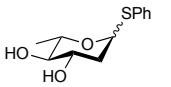
To a solution of 3,4-di-*O*-acetyl-L-rhamnal **38** (Chapter 2) (9.37 g, 54.0 mmol) in DCM (300 mL) were added acetic acid (5.10 mL, 5.39 g, 86.0 mmol, 1.6 eq) and PPh_3·HBr (2.20 g, 3.26 mmol, 0.1 eq). The reaction mixture was stirred for two days and concentrated *in vacuo.* Column chromatography (25:75 – 30:70 Et_2O:pentane) afforded the title compound as a white solid (7.63 g, 26.6 mmol, 51%, 5:1 α:β). Spectral data of the title compound was in accordance with that of literary precedence.[15]

Phenyl-3,4-di-*O*-acetyl-2-deoxy-1-thio-L-rhamnopyranoside (40)[15]



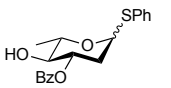
To a solution of **39** (7.6 g, 28 mmol) in DCM (200 mL) were added thiophenol (3.7 mL, 33 mmol, 1.2 eq) and BF_3·OEt_2 (4.9 mL, 33 mmol, 1.2 eq). The reaction mixture was stirred for 1 h, diluted with DCM and washed with sat. aq. $NaHCO_3$, 1M NaOH and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to obtain the title compound as a colorless oil (8.9 g, 28 mmol, quant., 1:1 α:β). Spectral data of the title compound was in accordance with that of literary precedence.

Phenyl-2-deoxy-1-thio-L-rhamnopyranoside (41)[15]



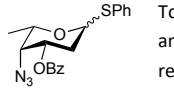
To a solution of **40** (9.9 g, 30 mmol) in MeOH (250 mL) was added sodium methoxide (330 mg, 6.11 mmol, 0.2 eq). After stirring for 2h, the reaction mixture was quenched by addition of dry ice. Solvent was removed *in vacuo* and the residue was coevaporated thrice with toluene. Column chromatography (50:50 – 100:0 Et_2O:pentane) afforded the title compound as a sticky pale yellow syrup (6.30 g, 26.3 mmol, 88%, 1:1 α:β). Spectral data of the title compound was in accordance with that of literary precedence.[15]

Phenyl-3-*O*-benzoyl-2-deoxy-1-thio-L-rhamnopyranoside (42)[15]



Diol **41** (5.89 g, 24.5 mmol) and dibutyltin dichloride (365 mg, 1.20 mmol, 0.05 eq) were dissolved in THF (125 mL). Benzoyl chloride (3.4 mL, 29 mmol, 1.2 eq) was added and the reaction mixture was stirred overnight. The reaction mixture was quenched by addition of 1M HCl and was subsequently partitioned between EtOAc and 1M HCl. The organic layer was washed with sat. aq. $NaHCO_3$ solution and brine, dried over Na_2SO_4 and solvent was removed *in vacuo*. Purification by column chromatography (30:70 Et_2O:pentane) afforded the title compound as a sticky syrup (7.10 g, 20.5 mmol, 84%, 3:2 α:β). Spectral data of the title compound was in accordance with that of literary precedence.[15]

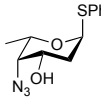
Phenyl-3-*O*-benzoyl-4-azido-2,4-deoxy-1-thio-L-fucopyranoside (43)



To a solution of **42** (5.20 g, 15.3 mmol) in DCM (150 mL) were added pyridine (15 mL) and triflic anhydride (2.3 mL, 18 mmol, 1.2 eq) at 0˚C. After stirring at that temperature for 15 minutes, the reaction was diluted with DCM and washed successively with 1M aq. $CuSO_4$ and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* at 0°C. The colorless oil thus obtained was dissolved in DMF (5 mL), to which NaN_3 (15.3 g, 37.5 mmol, 5 eq) was added, and the mixture was stirred overnight. The reaction mixture was then partitioned between H_2O and Et_2O, and the organic layer was washed with H_2O and brine and dried over $MgSO_4$. Solvent was removed *in vacuo* and purification by column chromatography (5:95 – 30:70 Et_2O:pentane) gave the title compound as a white solid (4.09 g, 11.1 mmol, 68%, 1:1 α:β). Spectral data for the α-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.16 – 8.05 (m, 2H), 7.64 – 7.54 (m, 1H), 7.51 – 7.41 (m, 4H), 7.35 – 7.20 (m, 3H), 5.72 (d, *J* = 5.8 Hz, 1H), 5.60 (ddd, *J* = 12.3, 4.7, 3.2 Hz, 1H), 4.58 (qd, *J* = 6.4, 1.5 Hz, 1H), 3.94 (dt, *J* = 3.0, 1.3

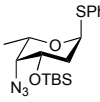
Hz, 1H), 2.63 (td, *J* = 12.8, 5.9 Hz, 1H), 2.25 (ddt, *J* = 13.2, 4.8, 1.2 Hz, 1H), 1.31 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7, 134.7, 133.7, 133.6, 131.1, 130.0, 129.3, 129.1, 128.7, 127.3, 83.7, 70.3, 66.1, 63.7, 30.9, 17.8. Spectral data for the β-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.12 – 8.04 (m, 2H), 7.65 – 7.49 (m, 3H), 7.49 – 7.38 (m, 2H), 7.38 – 7.19 (m, 3H), 5.33 (ddd, *J* = 11.3, 5.4, 3.4 Hz, 1H), 4.81 (dd, *J* = 11.2, 2.9 Hz, 1H), 3.80 (dt, *J* = 3.5, 1.1 Hz, 1H), 3.71 (qd, *J* = 6.3, 1.3 Hz, 1H), 2.49 – 2.09 (m, 2H), 1.39 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7, 133.7, 133.5, 132.0, 130.0, 129.2, 129.0, 128.6, 127.7, 82.4, 73.6, 72.8, 62.5, 31.5, 18.3. HRMS: $[M+Na]^+$ calculated for $C_{19}H_{20}O_4SNa$ 392.1039; found 392.1044.

Phenyl-4-azido-2,4-deoxy-1-thio-α-L-fucopyranoside (44)



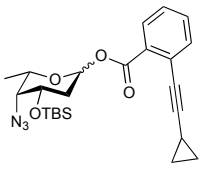
To a solution of **43α** (1.94 g, 5.25 mmol) in MeOH (200 mL) was added NaOMe until pH >10. After stirring overnight, the reaction mixture was quenched by addition of dry ice and solvent was removed *in vacuo*. Purification by column chromatography (10:90 - 50:50 Et_2O:pentane) afforded the title compound as a white solid (1.20 g, 4.52 mmol, 86%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 – 7.36 (m, 2H), 7.36 – 7.16 (m, 5H), 5.65 (d, *J* = 5.4 Hz, 1H), 4.48 (qdd, *J* = 6.5, 1.6, 0.6 Hz, 1H), 4.32 – 4.13 (m, 1H), 3.67 (dt, *J* = 3.1, 1.3 Hz, 1H), 2.27 (ddd, *J* = 13.4, 12.0, 5.8 Hz, 1H), 2.11 (ddt, *J* = 13.3, 4.9, 1.1 Hz, 1H), 1.92 (d, *J* = 7.8 Hz, 1H), 1.33 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.9, 131.1, 129.1, 127.3, 84.0, 67.2, 66.6, 66.6, 34.4, 17.9. HRMS: $[M-N_2+H]^+$ calculated for $C_{19}H_{20}NO_3S$ 238.0896; found 238.0903.

Phenyl-3-*O*-*tert*-butyldimethylsilyl-4-azido-2,4-deoxy-1-thio-L-fucopyranoside (45)



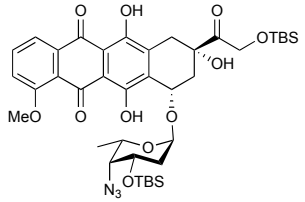
To a solution of **44** (318 mg, 1.20 mmol) in DMF (7.5mL), imidazole (204 mg, 1.80 mmol, 1.5 eq) and TBS-Cl (50 wt% in toluene, 0.20 mL, 2.4 mmol, 2 eq) were added and the reaction mixture was stirred for 3h. The reaction mixture was diluted with Et_2O, washed 4x with H_2O and once with brine, dried over $MgSO_4$ and solvent was removed *in vacuo*. Purification by column chromatography (5:95 Et_2O:pentane) afforded the title compound as a white solid (429 mg, 1.13 mmol, 94%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 – 7.37 (m, 2H), 7.33 – 7.20 (m, 3H), 5.64 (d, *J* = 5.7 Hz, 1H), 4.38 (qd, *J* = 6.3, 1.5 Hz, 1H), 4.28 (ddd, *J* = 11.8, 4.7, 3.3 Hz, 1H), 3.56 (dt, *J* = 2.9, 1.3 Hz, 1H), 2.43 (ddd, *J* = 13.5, 11.9, 5.8 Hz, 1H), 1.96 (ddt, *J* = 13.4, 4.7, 1.2 Hz, 1H), 1.25 (d, *J* = 6.4 Hz, 3H), 0.93 (s, 9H), 0.15 (d, *J* = 2.5 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 130.8, 129.1, 127.1, 84.2, 68.9, 66.4, 66.0, 34.8, 25.9, 18.0, -4.4. HRMS: $[M-N_2+H]^+$ calculated for $C_{24}H_{34}NO_4Si$ 352.1761; found 352.1772.

***o*-Cyclopropylethynylbenzoyl-3-*O*-*tert*-butyldimethylsilyl-4-azido-2,4-deoxy-L-fucopyranoside (46)**



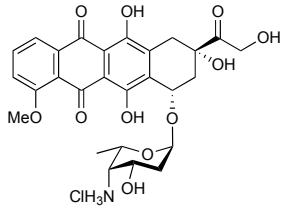
Thioglycoside **45** (410 mg, 1.09 mmol, 1 eq) was dissolved in THF/H_2O (6 mL, 9:1 v/v), to which $AgNO_3$ (648 mg, 3.82 mmol, 3.5 eq) was added. After stirring in the dark overnight under regular atmosphere, ethyl acetate (60 mL) and Na_2SO_4 were added and the reaction mixture was stirred for 1h, filtered over Celite and concentrated *in vacuo*. Column chromatography (20:80 Et_2O:pentane) afforded the crude hemiacetal. This was esterified according to general procedure B. Column chromatography (0:100 - 5:95 Et_2O:pentane) afforded the title compound as a colourless oil (297 mg, 0.598 mmol, 65%, 1:3 α:β). Spectral data for the β-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.98 (ddd, *J* = 8.0, 1.4, 0.6 Hz, 1H), 7.48 (ddd, *J* = 7.8, 1.6, 0.6 Hz, 1H), 7.42 (td, *J* = 7.5, 1.4 Hz, 1H), 7.33 – 7.26 (m, 2H), 5.88 (dd, *J* = 10.2, 2.5 Hz, 1H), 4.10 (ddd, *J* = 11.6, 4.8, 3.4 Hz, 1H), 3.69 (qd, *J* = 6.3, 1.4 Hz, 1H), 3.49 (dt, *J* = 3.4, 1.2 Hz, 1H), 2.16 (td, *J* = 11.9, 10.1 Hz, 1H), 2.01 (dddd, *J* = 12.3, 4.8, 2.5, 1.1 Hz, 1H), 1.57 – 1.45 (m, 1H), 1.35 (d, *J* = 6.4 Hz, 3H), 0.93 (s, 9H), 0.91 – 0.88 (m, 4H), 0.14 (d, *J* = 2.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 134.4, 132.2, 131.0, 130.7, 127.1, 125.3, 99.9, 92.6, 74.6, 71.0, 70.3, 65.1, 34.5, 25.8, 17.9, 9.0, 0.8, -4.4, -4.6. HRMS: $[M+Na]^+$ calculated for $C_{24}H_{33}N_3O_4SiNa$ 478.2133; found 478.2141.

7-[3-*O*-*tert*-butylsilyldimethylsilyl-4-azido-2,4-deoxy-α-L-fucopyranoside]-14-*O*-tert-butyldimethylsilyldoxorubicinone (47)



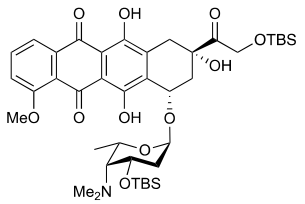
According to general procedure B, glycosyl donor **46** (266 mg, 0.585 mmol) was coupled to 14-O-*tert*-butyldimethylsilyl-doxorubicinone **18** (464 mg, 0.877 mmol, 1.5 eq). Column chromatography (15:85 Et_2O:pentane and then 1:99 - 10:90 acetone:toluene) of the residue gave the title compound as a red solid (440 mg, 0.551 mmol, 94%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.84 (s, 1H), 13.07 (s, 1H), 7.91 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.73 (dd, *J* = 8.4, 7.7 Hz, 1H), 7.36 (dd, *J* = 8.7, 1.1 Hz, 1H), 5.47 (d, *J* = 4.0 Hz, 1H), 5.18 (dd, *J* = 4.0, 2.1 Hz, 1H), 4.96 – 4.77 (m, 2H), 4.50 (s, 1H), 4.07 (s, 3H), 4.05 – 3.94 (m, 2H), 3.54 (d, *J* = 3.1 Hz, 1H), 3.09 (dd, *J* = 18.9, 1.8 Hz, 1H), 2.80 (d, *J* = 18.9 Hz, 1H), 2.25 (dt, *J* = 14.8, 2.1 Hz, 1H), 2.19 – 2.12 (m, 1H), 2.03 (ddd, *J* = 13.4, 11.8, 4.2 Hz, 1H), 1.83 – 1.69 (m, 1H), 1.31 (d, *J* = 6.4 Hz, 3H), 0.96 (s, 9H), 0.85 (s, 9H), 0.14 (d, *J* = 1.4 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.1, 186.8, 186.5, 161.0, 156.3, 155.6, 135.7, 135.3, 134.0, 133.8, 120.7, 119.8, 118.5, 111.3, 111.3, 101.3, 77.5, 77.3, 77.2, 76.8, 69.6, 67.9, 66.6, 66.1, 56.7, 35.5, 34.0, 33.8, 25.9, 25.7, 18.7, 18.1, 18.0, -4.4, -4.7, -5.2, -5.3. HRMS: $[M+Na]^+$ calculated for $C_{39}H_{55}N_3O_{11}Si_2Na$ 820.3267; found 820.3287.

3'-Desamino-3'-hydroxy-4'-deoxy-4'-aminodoxorubicin hydrochloride (isodoxorubicin hydrochloride) (10)



To a solution of **47** (110 mg, 0.138 mmol, 1 eq) in THF/H_2O (20 mL, 10:1 v/v) was added triphenylphosphine (108 mg, 0.412 mmol, 3 eq) and the reaction mixture was stirred for a week at 50 °C. Solvent was removed *in vacuo* and the residue was subjected to column chromatography (30:70 EtOAc:pentane, then 10:90 – 20:80 acetone:toluene) to give the crude amine **48**. The amine thus obtained was desilylated using HF·pyridine (70 wt% HF, 0.24 mL) according to general procedure C. Column chromatography on neutral silica (0:100 – 10:90 MeOH:DCM) afforded the title compound as a red solid (27 mg, 49.7 µmol, 36% over 2 steps). The corresponding HCl salt was prepared by lyophilization from aqueous 10 µM HCl (1 mL/µmol, 2 eq). ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 14.06 (s, 1H), 13.26 (s, 1H), 7.92 (q, *J* = 4.0, 3.2 Hz, 2H), 7.87 – 7.75 (m, 3H), 7.71 – 7.62 (m, 1H), 5.69 (d, *J* = 26.2 Hz, 1H), 5.51 (s, 1H), 5.29 (d, *J* = 3.9 Hz, 1H), 4.95 (t, *J* = 4.5 Hz, 1H), 4.58 (s, 2H), 4.37 (q, *J* = 6.5 Hz, 1H), 3.99 (s, 5H), 3.19 (d, *J* = 27.2 Hz, 2H), 3.05 – 2.88 (m, 2H), 2.12 (d, *J* = 4.4 Hz, 2H), 1.75 (dd, *J* = 13.5, 5.4 Hz, 1H), 1.65 (td, *J* = 13.1, 4.0 Hz, 1H), 1.21 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, DMSO) δ 213.9, 186.6, 186.6, 160.8, 156.0, 154.4, 136.3, 135.1, 134.7, 134.2, 120.0, 119.8, 119.1, 110.8, 100.2, 74.8, 70.2, 63.7, 63.0, 61.5, 56.6, 54.1, 36.5, 32.4, 32.0, 16.9. HRMS: $[M+H]^+$ calculated for $C_{27}H_{30}NO_{11}$ 544.1813; found 544.1816.

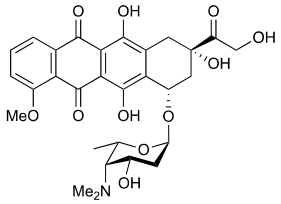
7-[3-*O*-*tert*-butyldimethylsilyl-4-dimethylamino-2,4-deoxy-α-L-fucopyranoside]-14-*O*-tert-butyldimethylsilyldoxorubicinone (49)



To a solution of **47** (130 mg, 0.160 mmol, 1 eq) in THF/H_2O (26 mL, 10:1 v/v) was added triphenylphosphine (129 mg, 49 mmol, 3 eq) and the reaction mixture was stirred for four days at 50 °C. Solvent was removed *in vacuo* and the red residue was subjected to column chromatography (1:99 – 15:85 acetone:toluene). To the amine **48** thus obtained (65 mg, 83 µmol) in EtOH (6.8 mL) were added aq. CH_2O (aq. 37% w/v, 0.20 mL, 30 eq) and $NaBH(OAc)_3$ (34.6 mg, 16.4 mmol, 1.95 eq). The reaction mixture was stirred for two hours and partitioned between DCM and sat. aq. $NaHCO_3$. The aqueous layer was extracted thrice with DCM and combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (1:199 - 5:95 acetone:toluene) afforded the title compound as a red solid (55 mg, 69 µmol, 43% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.90 (s, 1H), 13.23 (s, 1H), 8.00 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.76 (dd, *J* = 8.5, 7.7 Hz, 1H), 7.38 (dd, *J* = 8.6, 1.2 Hz, 1H), 5.51 (t, *J* = 4.0 Hz, 1H), 5.26 (dd, *J* = 3.9, 2.2 Hz, 1H), 5.02 – 4.83 (m, 2H), 4.78 (s, 1H), 4.20 (ddq, *J* = 18.2, 9.1, 4.5, 4.1 Hz, 2H), 4.09 (s, 3H), 3.17 (dd, *J* = 19.0, 1.9 Hz, 1H), 2.97 (d, *J* = 18.9 Hz, 1H), 2.53 (s, 6H), 2.47 (t, *J* = 2.1 Hz, 1H), 2.42 – 2.34 (m, 1H), 2.16 – 2.04 (m, 2H), 1.96 (s, 1H), 1.69 (dt, *J* = 13.7, 4.5 Hz, 1H),

1.40 (d, *J* = 6.7 Hz, 3H), 0.96 (s, 9H), 0.90 (s, 9H), 0.14 (d, *J* = 2.8 Hz, 6H), 0.05 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.9, 187.1, 186.7, 161.1, 156.5, 156.0, 135.7, 135.6, 134.6, 134.1, 121.1, 119.9, 118.5, 111.5, 111.4, 99.6, 77.3, 70.1, 69.7, 69.2, 66.8, 65.4, 56.8, 44.9, 37.7, 35.4, 34.0, 26.0, 18.7, 18.1, 17.1, -4.3, -4.6, -5.1, -5.2. HRMS: [M+H$^+$] calculated for $C_{41}H_{62}NO_{11}Si_2$ 800.3861; found 800.3852.

***N,N*-dimethylisodoxorubicin (11)**



49 (29 mg, 36 µmol) was desilylated using HF·pyridine (70 wt% HF, 0.14 mL) according to general procedure C. Column chromatography on neutral silica (0:100 – 95:5 MeOH:DCM) afforded the title compound as a red solid (15 mg, 26 µmol, 72%). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 13.92 (s, 1H), 13.22 (s, 1H), 8.01 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.77 (dd, *J* = 8.4, 7.7 Hz, 1H), 7.39 (dd, *J* = 8.5, 1.1 Hz, 1H), 5.55 (t, *J* = 4.2 Hz, 1H), 5.30 (dd, *J* = 3.9, 2.2 Hz, 1H), 4.81 (s, 1H), 4.77 (d, *J* = 1.3 Hz, 2H), 4.29 (qd, *J* = 7.0, 3.8 Hz, 1H), 4.08 (s, 3H), 3.94 (dt, *J* = 9.0, 4.8 Hz, 1H), 3.24 (dd, *J* = 18.9, 2.0 Hz, 1H), 2.99 (d, *J* = 18.8 Hz, 1H), 2.54 (s, 6H), 2.49 – 2.43 (m, 2H), 2.12 (dd, *J* = 14.7, 3.9 Hz, 1H), 1.91 (ddd, *J* = 14.0, 8.5, 3.8 Hz, 1H), 1.78 (dt, *J* = 14.0, 4.8 Hz, 1H), 1.52 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.4, 187.1, 186.8, 161.2, 156.4, 155.8, 135.8, 135.6, 134.0, 133.8, 121.1, 119.9, 118.6, 111.7, 111.6, 99.1, 70.0, 69.4, 65.7, 64.4, 64.0, 56.8, 44.7, 35.9, 35.4, 34.1, 17.4. HRMS: [M+H]$^+$ calculated $C_{29}H_{35}NO_{11}$ for 572.2126; found 572.2142.

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Chapter 6

Summary and future prospects

Since its isolation in 1969, the anthracycline doxorubicin (**1**) has become one of the most oft-used anti-cancer drugs, this in spite of its cardiotoxicity. More than a thousand analogs have been isolated from nature and prepared by organic synthesis, but the vast majority of these compounds did not outperform doxorubicin in terms of efficacy and cardiotoxicity. The exception appeared to be aclarubicin (**2**), which is much less cardiotoxic, however this close structural analog of doxorubicin is currently not in clinical use outside China and Japan. It has recently been shown that both anthracyclines **1** and **2** are able to induce eviction of histones from chromatin, and it has been hypothesized this is the main mode of action behind antitumor activity.

The work described in this Thesis entails the synthesis of anthracyclines inspired by the structures of doxorubicin and aclarubicin, with the aim to establish structure-activity relationships for these compounds. To this end, hybrid structures featuring structural elements of both anthracyclines have been prepared, as well as regioisomers, stereoisomers and other derivatives of doxorubicin. These should ultimately allow for the design of anthracyclines with reduced cardiotoxicity and better efficacy.

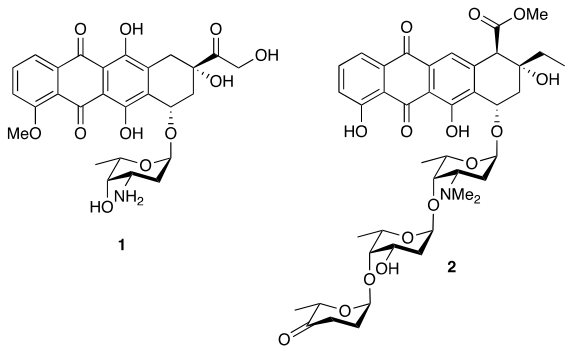


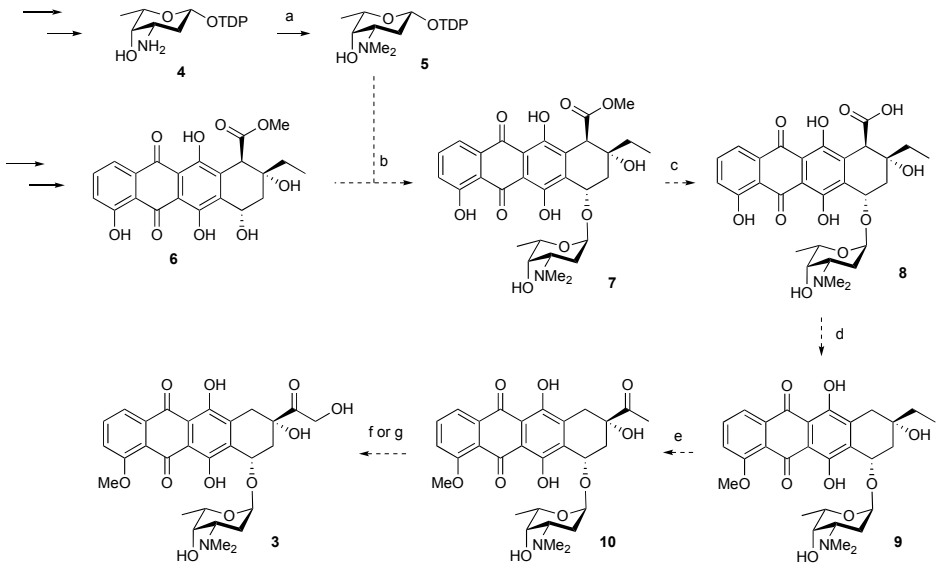
Figure 1. Structures of doxorubicin (**1**) and aclarubicin (**2**).

Chapter 1 presents a historical overview of the discovery of the first anthracyclines and their use in cancer treatment, and discusses some relevant routes of synthesis of 2-deoxyglycosides and anthracyclines.

Studies towards the synthesis of *N,N*-dimethyldoxorubicin are described in **Chapter 2**. This hybrid anthracycline combines structural elements from doxorubicin and aclarubicin. Since direct reductive alkylation of the amine in (semi-protected) doxorubicin led to undesired reduction of the ketone functionality, a new strategy had to be developed that is based on the glycosylation of an appropriately protected tetracycline aglycon with an orthogonally protected *ortho*-alkynylbenzoate glycosyl donor using the gold(I)-glycosylation chemistry developed by the group of Yu. This strategy proved fruitful, and the gold-promoted glycosylation proceeded with excellent α-stereoselectivity. The choice for a 4'-triethylsilyl protecting group facilitated the reductive alkylation whilst leaving the ketone intact, and final deprotection yielded *N,N*-dimethyldoxorubicin.

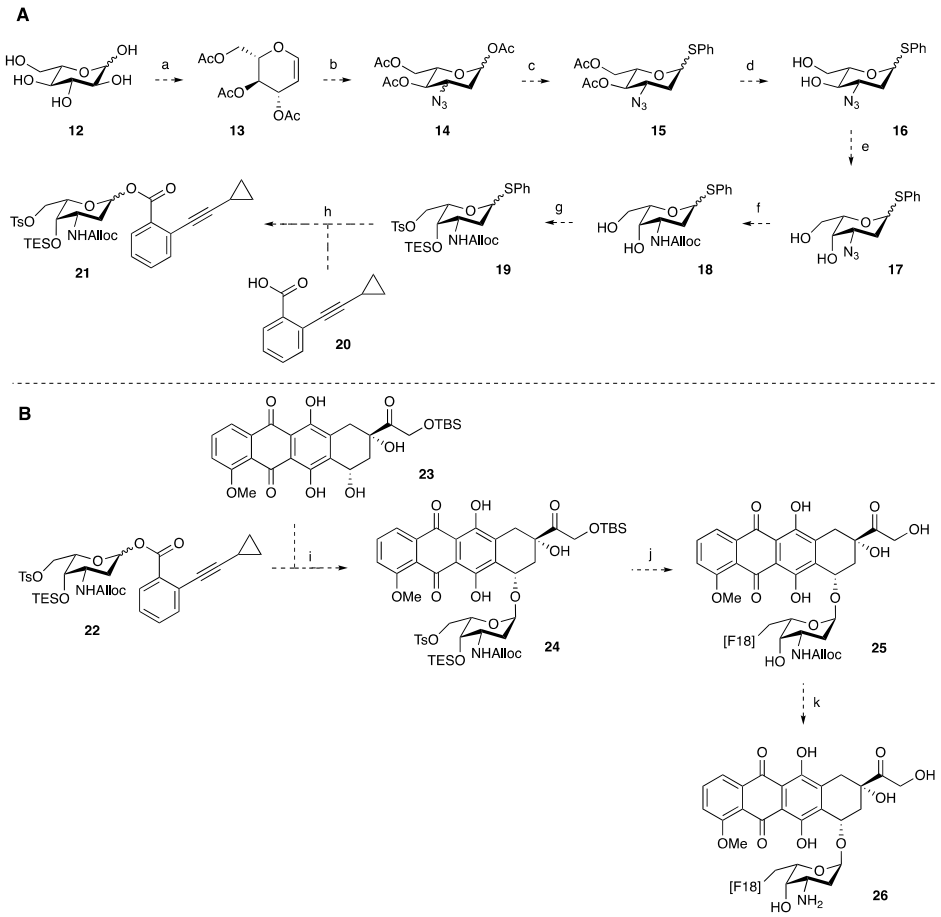
Although a large variety of anthracyclines are readily available through organic synthesis, their eventual use as anti-cancer drugs would require much larger quantities than those that can be generated through the here-described synthetic routes at competitive costs. Clinical doxorubicin is currently prepared through fermentation by a *Streptomyces peucetius* mutant, followed by chemical 14-hydroxylation. A chemo-enzymatic synthesis of *N,N*-dimethyldoxorubicin could also be envisaged, as outlined in Scheme 1. The combination of two or more biosynthetic pathways has been used in combinatorial biosynthesis approaches to obtain compounds that are not enzymatically produced or generated in minimal amounts. This concept has been used in the production of modified complex polyketides[1] and has already been applied to *S. galilaeus.*[2] In the biosynthesis of aclarubicin by *S. galilaeus*, dimethylation of the amine in TDP-daunosamine is performed by the aminomethylase enzyme *aknX2*.[3] Expression of this enzyme and the corresponding rhodosaminyl transferase into *S. peucetius* could enable the biosynthesis of *N,N*-dimethyldoxorubicin. In a similar manner, additional doxorubicin and aclarubicin inspired structures as described in Chapter 3 that could be prepared through manipulation of anthracycline biosynthesis machineries.

It would also be of interest to study the biodistribution of anthracyclines in the body using PET imaging. This has been done in the past using [18F]-labeled micelles[5,6] and nanoparticles[7] carrying doxorubicin as the toxic payload, but not on the stand alone drugs. As 14-fluorinated daunorubicin was shown to be a tenfold less potent than its parent compound,[8] [18F]-labelled doxorubicin (**11**) might be a better alternative. This compound would bear an [18F]-moiety on the 6-position of the sugar. 6',6',6'-Trifluoro-hydroxyrubicin has earlier been shown to exhibit higher potency against murine leukemia P388 than its parent compound,[9] and the modification in **11** is therefore expected to be well tolerated in terms of activity.



Scheme 1. Proposed biosynthesis of *N,N*-dimethyldoxorubicin (**3**) by mutant *S. peucetius*. (a) Dimethylation of TDP-daunosamine by *AknX2*; (b) Glycosylation on C-7 by rhodosaminyl transferase; (c) Demethylation of the acid at C-10 (*DnrP*); (d) Decarboxylation and methylation of the C-4 phenol (*DnrK*); (e) Oxidation at C-13 (*DoxA*); (f) Chemical hydroxylation of C-14 by *i.* Bromination of C-14; *ii.* Hydrolysis; (g) Enzymatic hydroxylation at C-14 by enzymatic overexpression of *DoxA*, as in mutant ATCC 27952.[4]

The synthesis of the envisaged 6-hydroxydaunosaminyl donor **21** would commence from L-glucose **12** in Scheme 2A, which can easily be obtained in 5 steps from cheap and commercially available sodium α-D-glucoheptonate.[10] This would then be converted to L-glucal **13** by means of peracetylation, anomeric bromination and Zn/Cu-mediated elimination of the 1-bromide and 2-*O*-acetate. Using the chemistry described in Chapter 2, mixture of azides **14** would be obtained. Installation of an anomeric thiophenyl moiety, followed by deacylation would yield diol **16**. Inversion of the 4-position would be accomplished by triflation of both the 4- and 6-hydroxyl groups, followed by reaction with tetrabutylammonium nitrate to yield *galacto*-conformed diol **17**. The azide would then be switched for an Alloc group, after which tosylation of the primary alcohol and silylation of the secondary alcohol would yield **19**. Silver-mediated hydrolysis of the anomeric thiophenyl group, followed by esterification to *ortho*-cyclopropylethynylbenzoic acid **20** would yield alkynylbenzoate donor 21. Glycosylation under Yu's gold(I)-catalyzed conditions would then give **24** (Scheme 2B). At this stage, treatment with [18F]KF·K_{222} would substitute the tosylate for the desired [18F]-moiety,[11] as well as remove the silyl ethers. Final removal of the Alloc group would yield 6'-[18F]-doxorubicin **11**.

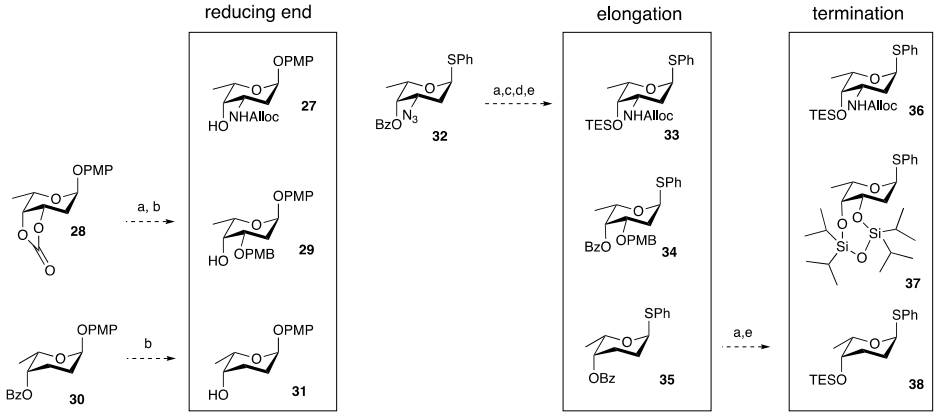


Scheme 2. Proposed synthesis of 6'-[18F]-doxorubicin (**11**). *Reagents and conditions:* (a) *i.* Ac_2O, NaOAc, 140 °C; *ii.* HBr/AcOH, Ac_2O, DCM; *iii.* Zn, AcOH, NaOAc, Ac_2O, $CuSO_4{\cdot}5H_2O$, MeCN; (b) *i.* H_2O, 80 °C, then NaN_3, AcOH; *ii.* Ac_2O, pyr.; (c) thiophenol, $BF_3{\cdot}OEt_2$, DCM, -78 °C to 0 °C; (d) NaOMe, MeOH; (e) *i.* Tf_2O, pyr., DCM, 0°C; *ii.* $TBANO_2$, MeCN; (f) polymer-bound PPh_3, THF, H_2O, then Alloc-OSu, $NaHCO_3$; (g) *i.* TsCl, pyr., DCM, -20 °C; then TESOTf, pyr., -20 °C; (h) *i.* $AgNO_3$, 2,6-lutidine, THF/H_2O; *ii.* EDCI·HCl, DIPEA, DMAP, DCM; (i) PPh_3AuNTf_2 (10 mol%), DCM; (j) [18F]KF·K_{222}, K_2CO_3, DMSO; (k) $Pd(PPh_3)_4$, NDMBA, DCM.

Chapter 3 describes the synthesis of a library of nine doxorubicin/aclarubicin hybrid structures, filling the chemical space between these two anthracyclines. The assembly of these compounds relied on the use of Yu's *ortho*-alkynylbenzoate glycosylation method explored in Chapter 2 to construct the α-glycosidic bond between the respective aglycone and mono-/di-/trisaccharide moieties. The relevant di- and trisaccharide donors were assembled by (iterative) α-selective IDCP-mediated glycosylation reactions, and the anthracycline aglycones were obtained from acidic hydrolysis of the parent anthracyclines. Further highlights in these syntheses are the orthogonal removal of the anomeric *p*-methoxyphenolate over the PMB group present

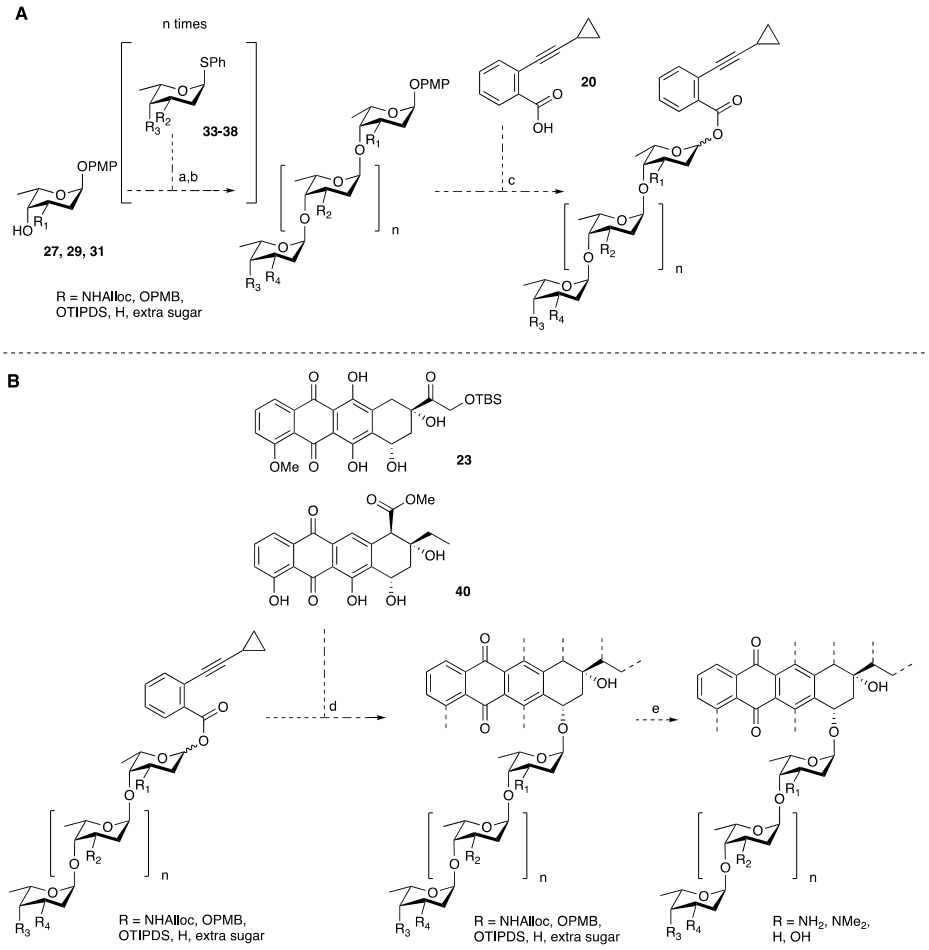
on the oliose moiety and the *post*-glycosylation introduction of the dimethylamine functionality.

It would be of interest to investigate the influence of switching the order of the sugars (rhodosamine, oliose, cinerulose A) in the trisaccharide found in aclarubicin on the biological activities of the resultant compounds. Additionally, longer chains (4 or more sugars) could be envisaged. To this end, nine monosaccharide building blocks are envisaged, as depicted in Scheme 3.



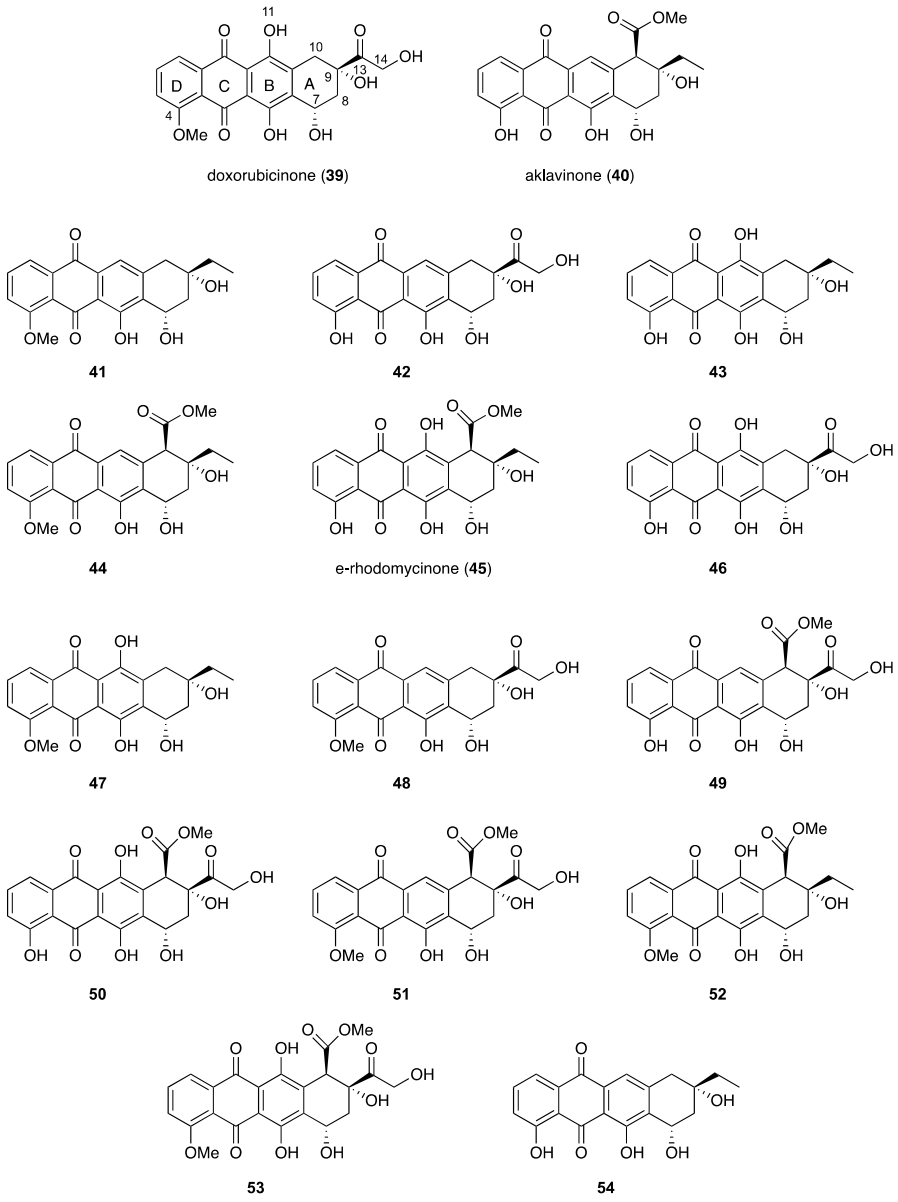
Scheme 3. Building blocks for aclarubicin-inspired sugar chain in different sugar order. *Reagents and conditions:* (a) NaOMe, MeOH; (b) *i.* Bu_2SnO, tol., 100 °C; *ii.* PMB-Cl, TBABr, tol.; (c) PPh_3, THF, H_2O, 50 °C; (d) Alloc-OSu, $NaHCO_3$, THF, H_2O; (e) TESOTf, pyr., DCM.

One of each of the three sugars is designed to be at the reducing end of the protected trisaccharides to give glycosyl acceptors **27**, **29** and **31**. These all feature a *p*-methoxyphenyl group at the reducing end, and a free hydroxyl group on the 4-position. As cinerulose A features a ketone on the 4-position and would not allow for further glycosylation, it is replaced by rhodinose. The three thioglycosides **33**, **34** and **35** serve as donors for elongation of the saccharide chain. They all feature a bulky group on the 4-position that should facilitate α-selective glycosylation. Finally, thioglycosides **36**, **37** and **38** could serve as the end of the chain and are protected with silyl ethers that can be deblocked after glycosylation to the desired aglycone.



Scheme 4. Glycosylations and deprotections for aclarubicin-inspired sugar chain in different sugar order. *Reagents and conditions:* (a) *i.* IDCP, Et_2O, DCE (4:1 v/v); *ii.* NaOMe, MeOH for benzoyl esters, HF·pyridine, pyr. for silyl ethers; c) *i.* Ag(II)(hydrogen dipicolinate)$_2$, NaOAc, MeCN, H_2O, 0 °C; *ii.* EDCI·HCl, DIPEA, DMAP, DCM; (d) PPh_3AuNTf_2 (10 mol%), DCM; (e) HF·pyridine, pyr. for silyl ethers; $Pd(PPh_3)_4$, NDMBA, DCM for Alloc groups; DDQ, DCM/pH 7 phosphate buffer for PMB ethers; aq. CH_2O, $NaBH(OAc)_3$, EtOH for demethylation.

As in Chapter 3, iterative IDCP glycosylation and deblocking would then yield the protected saccharides (Scheme 4). The initially chosen acceptor at the reducing end (**27**, **29**, or **33**) can be elongated *n*-times with thioglycoside donors **33**, **34** and **35** and finally terminated with **36**, **37** or **38** to achieve the desired saccharide chain length and composition. Finally, the *p*-methoxyphenolate would be removed oxidatively, followed by esterification to yield the corresponding *ortho*-alkynylbenzoate donors. Glycosylation to the desired aglycone is then followed by global deprotection and, if desired, reductive dimethylation onto the amine to yield the target compounds.

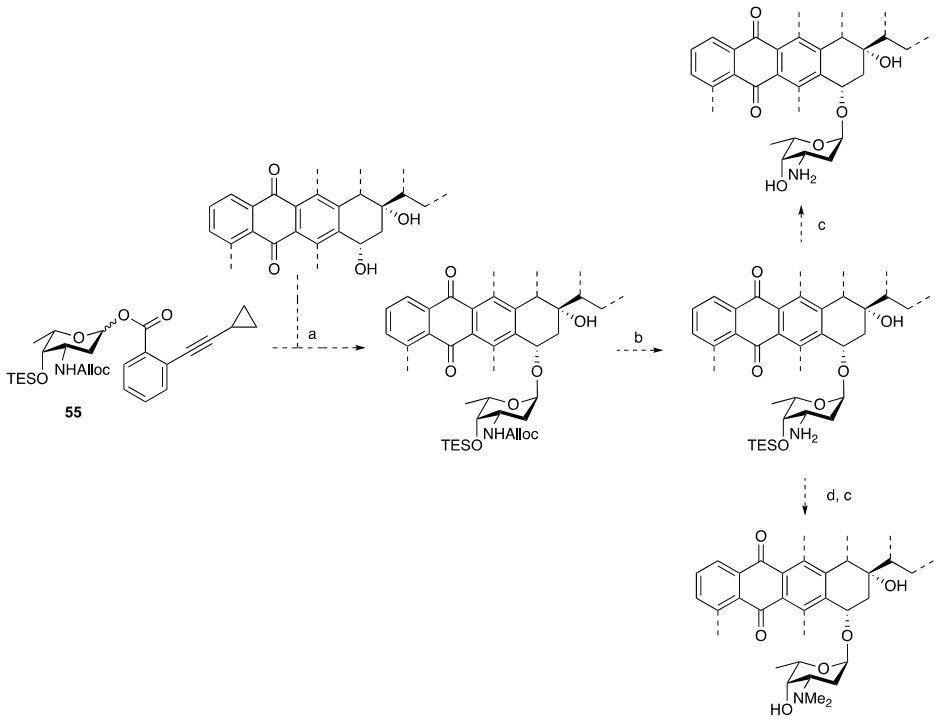


Scheme 5. Doxorubicinone (**39**), aklavinone (**40**) and hybrid aglycones **41-54**, aimed to fill the chemical space between these two anthracyclines.

As Chapter 3 explored the chemical space of the saccharides found in doxorubicin and aclarubicin, it would be of interest to prepare variants differing in their aglycone moieties as well. The chemical differences between doxorubicinone and aklavinone can be divided into 4 mutations: methylation of the 4-phenolate, hydroxylation of the 11-

position, presence/absence of a methyl ester on the 10-position and the oxidation pattern of the 9-ethyl tail. In this manner, 2^4 = 16 aglycones can be envisaged, which are depicted in Scheme 5.

These aglycones would be obtained through (manipulation of) the biosynthetic pathways of known anthracyclines, or chemical derivatization. These aglycones could then be glycosylated to the daunosamine donor described in Chapter 3 (see Scheme 6) to yield the corresponding hybrid anthracyclines. Deprotection of the Alloc group can either be followed by global desilylation, or first be subject to reductive dimethylation and then desilylation to yield the anthraquinone daunosamines or rhodosamines.



Scheme 6. Proposed synthesis of anthracyclines with different aglycones. *Reagents and conditions:* (a) PPh_3AuNTf_2 (10 mol%), DCM; (b) $Pd(PPh_3)_4$, NDMBA, DCM; (c) HF·pyridine, pyr.; (d) aq. CH_2O, $NaBH(OAc)_3$, EtOH.

Chapter 4 describes the synthesis of a series of analogs of doxorubicin that differ in the nature of the functionality at the 3'-position. These include neutral 3'-analogs (lacking the basic amine), 3'-methyl analogs that introduce steric bulk onto the daunosamine ring, singly *N*-methylated and doubly *N*-ethylated doxorubicin and finally *N*-heterocyclic doxorubicins. The latter series were prepared in a single step from doxorubicin,

whereas the other compounds were assembled from the relevant *ortho*-alkynylbenzoate donors and protected doxorubicinone. Rather than preparing the glycosides through deoxygenation and amination of L-fucose or L-rhamnose, certain rare sugars can also be obtained from natural source, a strategy applied for the synthesis of the 3'-methyl-doxorubicins. Methanolysis of vancomycin facilitated the isolation of its sugar moiety vancosamine, which could be appropriately functionalized and appended to the doxorubicinone aglycone.

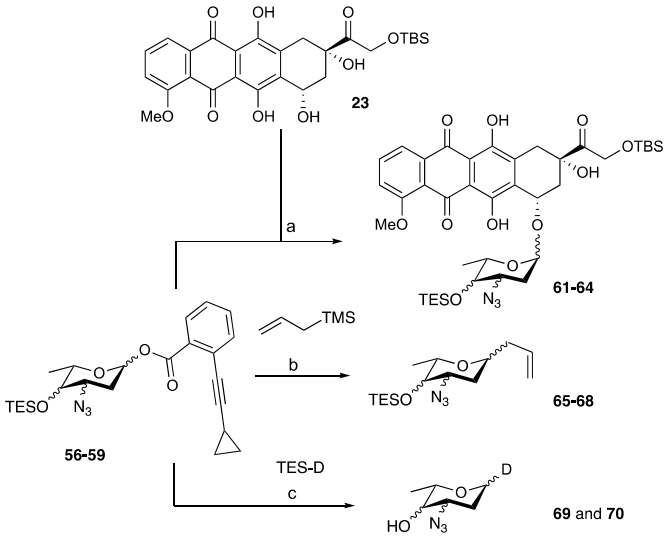
Chapter 5 describes the synthesis of stereo- and regio-isomers within the aminosugar moiety of doxorubicin. Epimers of the 3'- and 4'- position were prepared, along with their *N,N*-dimethylated variants. Additionally, switching the 3'- and 4'-position yielded two *iso*-doxorubicins.

The glycosylations of the aminosugar donors to the doxorubicin aglycone in this Chapter proceeded with varying stereoselectivity, and it would be beneficial to gain further insight into the underlying glycosylation reaction mechanism. To this end, a method by Hansen *et al.* (Figure 2) was applied that allows for direct comparative quantification of the stereoselectivity of the reactive intermediates (oxocarbenium ions) through DFT calculations, as a function of the conformation of these ions.[12–14] Through this computational method, globes are generated which depict the conformational energy landscape (CEL) for the corresponding oxocarbenium ion generated from the glycosyl donor of choice. The energy minima computed in this fashion are then divided between top- and bottom face selective families to give an α:β ratio that can be compared to that obtained in the corresponding chemical glycosylation reactions employing triethylsilane of allyl-TMS as nucleophiles.

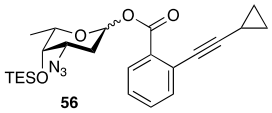
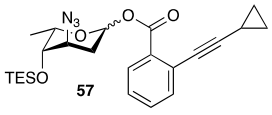
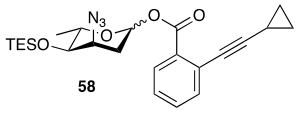
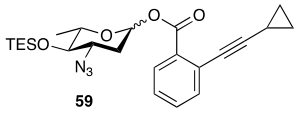
Thus, daunosamine, 3-epidaunosamine, ristosamine and acosamine donors used in Chapter 2 and 5, alkynylbenzoate donors **56**-**59** were prepared and subjected to gold(I)-catalyzed glycosylation to nucleophiles allyltrimethylsilane (allylTMS) and 14-*O*-TBS-doxorubicinone **23**. AllylTMS is a weak nucleophile, that generally does not react following an S_N2-type displacement mechanism.[15,16]

This computational model has not yet been used to probe the influence of (long range) neighboring group participation and therefore the amines in the donors are protected as an azide rather than the Alloc carbamate used in Chapter 5. Furthermore, the TES group was replaced by a TMS group to decrease the required computational costs. The results of the glycosylations performed with these four donors **56-59** as well as the computed stereoselectivities are shown in Table 3.

Table 1. Glycosylation stereoselectivities of *ortho*-alkynylbenzoate donors **56**-**59** to 14-*O*-TBS-doxorubicinone (**23**), allylTMS and TES-D, and *in silico* modelled α:β ratio based on oxocarbenium ion conformations.



Reagents and conditions: (a) 14-*O*-TBS-doxorubicinone (**23**) (1.5 eq), PPh_3AuNTf_2, 0.05M in DCM, RT; **(b)** allylTMS (8 eq), PPh_3AuNTf_2, 0.05M in DCM. The glycosylations with TES-D required stoichiometric amounts of gold catalyst and the resultant products were isolated as their 4-alcohols.

Entry	Donor	Acceptor **23** α:β-ratio (yield)	AllylTMS α:β-ratio (yield)	TES-D α:β-ratio (yield)	*In silico* computed α:β ratio
1	 **56**	>98:2 (79%)	>98:2 (67%)	-	>98:2
2	 **57**	>98:2 (84%)	>98:2 (83%)	-	>98:2
3	 **58**	75:25 (78%)	>98:2 (66%)	93:7 (83%)	83:17
4	 **59**	75:25 (91%)	≥90:10 (60%)	66:34 (78%)	41:59

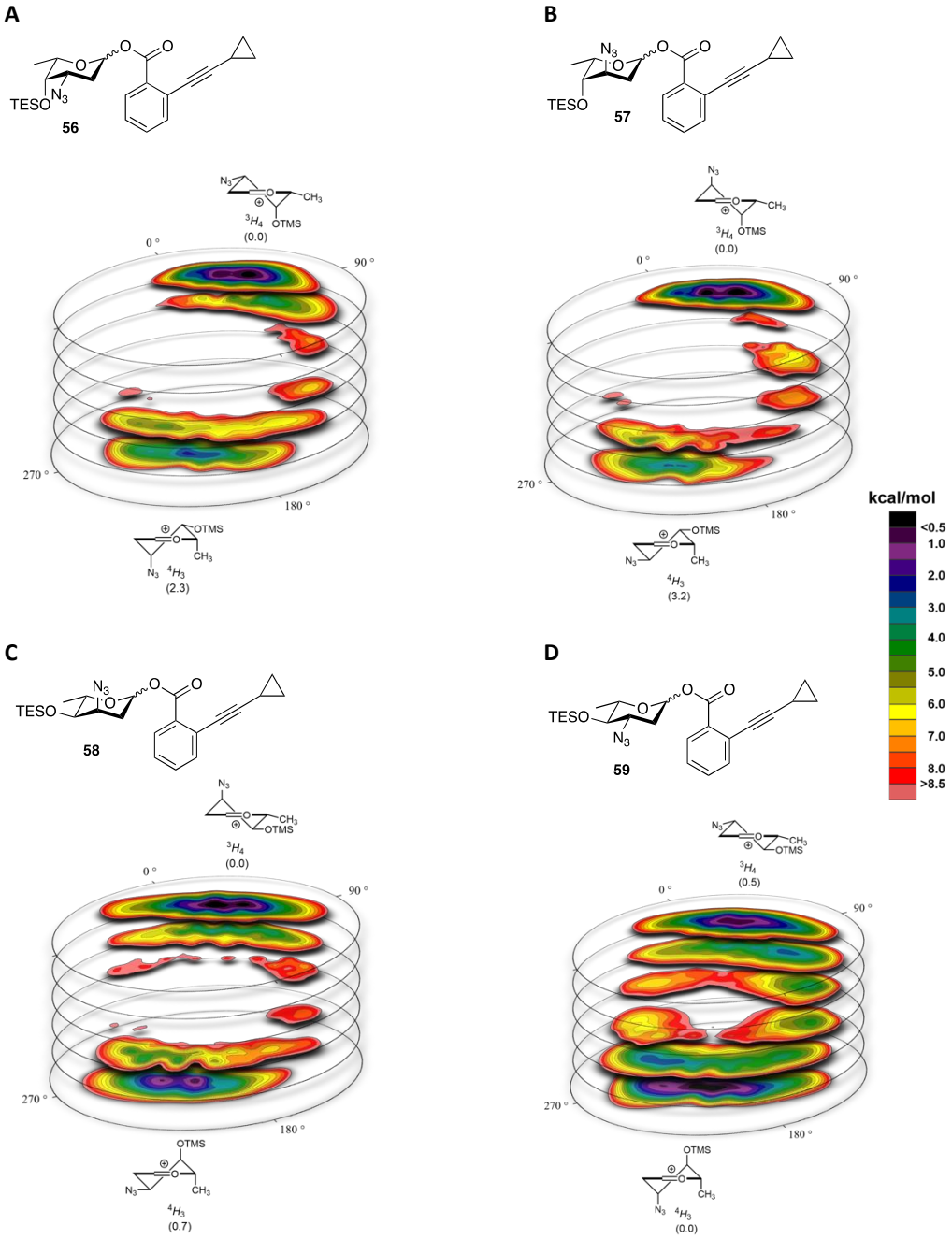


Figure 3. CEL maps of oxocarbenium ions in which the found local minima are indicated with their respective energies. (**A**) CEL map of daunosaminyl donor **56** derived oxocarbenium ions; (**B**) CEL map of 3-*epi*-daunosaminyl donor **57** derived oxocarbenium ions; (**C**) CEL map of ristosaminyl donor **58** derived oxocarbenium ions; (**D**) CEL map of acosaminyl donor **59** derived oxocarbenium ions.

Glycosylation of daunosaminyl donor **56** and 3-*epi*-daunosamine **57** to doxorubicinone-acceptor **23** as well as allylTMS under the agency of PPh_3AuNTf_2 proceeded in excellent stereoselectivity (>98:2). The *in silico* generated CEL maps for the oxocarbenium ions derived from these donors are shown in Figure 3A and 3B. Both feature clear energy minima for the $^3H_4$ oxocarbenium ions, which upon top-side attack yield the corresponding α-glycosides. The computed stereoselectivity predicted by these maps is a >98:2 mixture, in perfect agreement with the experimental glycosylation. Ristosamine donor **58** gave a 75:25 α:β mixture upon glycosylation to acceptor **23**, but proceeded α-selectively when using allylTMS as the acceptor instead. As this discrepancy may be the result of steric factors induced by the weak nucleophile allylTMS, the model glycosylation was also performed using TES-D as the nucleophile to yield a 93:7 mixture. In this case, a stoichiometric amount of gold(I) catalyst was required to drive the reaction to completion and the product was obtained without the silyl ether. The CEL map generated for the ristosaminyl oxocarbenium ions shows two relevant energy minima both for the $^3H_4$ and the $^4H_3$ conformations (0.7 kcal/mol difference in favor of $^3H_4$), predicting a 75:25 α:β mixture. The coupling of acosamine donor **59** to acceptor **23** proceeded with moderate stereoselectivity (3:1 α:β), whereas the coupling to allylTMS gave a 9:1 α:β mixture instead. Conversely, the CEL method gave two distinct energy minima (0.5 kcal/mol difference in favor of $^4H_3$), predicting the addition reaction to be slightly β-selective (41:59). Subjection of this donor to TES-D and a stoichiometric amount of PPh_3AuNTf_2 yielded a 66:34 mixture of anomers. Discrepancy between the ratio as predicted by the CEL method and the selectivities found in the experiment can be attributed to several factors. First, the reactive intermediates generated during gold(I)-mediated glycosylation of *ortho*-alkynylbenzoates are likely not the bare oxocarbenium ions. Furthermore, the relatively high temperature at which these glycosylations were performed (25 °C) may allow S_N2-like pathways to occur.

Overall, it appears that the computational method is able to give an indication of the stereoselectivity obtained in glycosylations with 2,3,6-dideoxy-3-azido alkynylbenzoate donors. It was shown that daunosaminyl- and 3-*epi*-daunosaminyl oxocarbenium ions give 1,5-*trans*-selective glycosylation, in line with the computed ratio, and that ristosaminyl- and acosaminyl are predicted to – and proceed – in an aselective fashion. Furthermore, the *C*-allyl glycosides obtained could be used to prepare more stable counterparts of commonly unstable 2-deoxy *O*-glycosides.

Within the context of regioisomers of doxorubicin, fucosamine-doxorubicinones **71** and **72** were envisaged (Figure 4). In these compounds, the amine function is shifted to the 2-position with respect to doxorubicin. Additionally, elongation of **71** with the terminal disaccharide found in aclarubicin was envisaged to yield trisaccharide **73**.

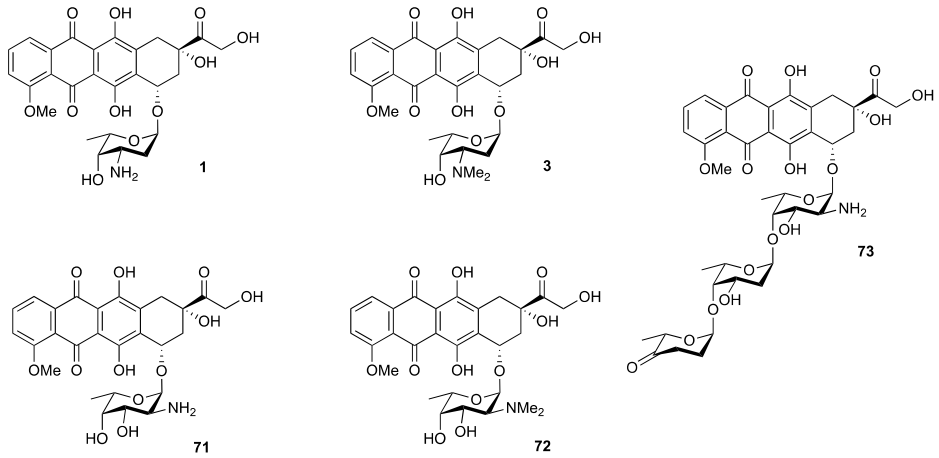
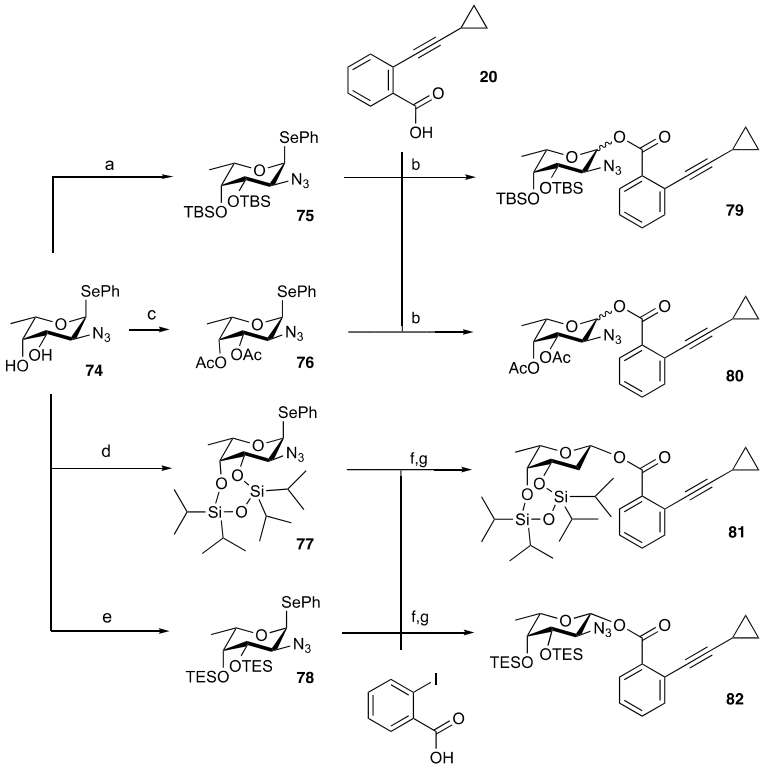


Figure 4. Doxorubicin (**1**) and *N,N*-dimethyldoxorubicin (**3**), in addition to their regio-isomers fucosamine-doxorubicinones **71** and **72** and trisaccharide **73**.

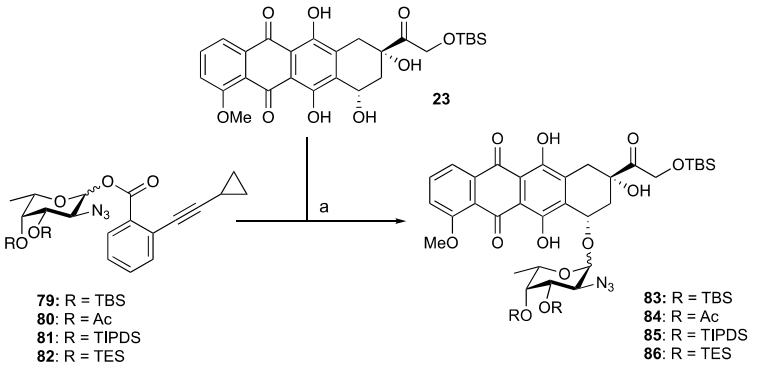
The synthesis of alkynylbenzoates **79**-**82** in Scheme 7 commenced with L-azidoselenofucoside **74**, prepared according to Hagen *et al*.[17] This diol was then protected with TBS, TES, acetyl or TIPDS groups to yield **75**-**78**. TBS and acetyl protected selenides **75** and **76** were then subjected to NIS-mediated hydrolysis, after which the hemiacetals were esterified to *ortho*-cyclopropylethynylbenzoic acid **20** to yield the corresponding anomeric alkynylbenzoates. This same procedure proved very low yielding for TES- and TIPDS-protected **77** and **78**, and these were subjected to esterification to iodobenzoic acid instead. Final Sonogashira coupling to cyclopropylacetylene yielded the *ortho*-alkynylbenzoates **79**-**82**.



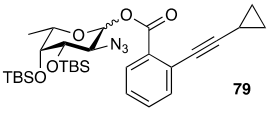
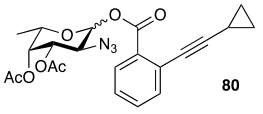
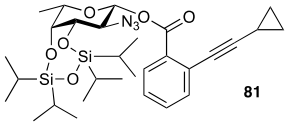
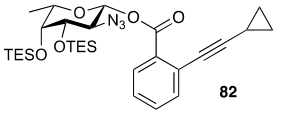
Scheme 7. Synthesis of four fucosazide *ortho*-alkynylbenzoate donors **79**-**82**. *Reagents and conditions:* (a) TBSOTf, pyr., DMF, 0 °C to RT, quant.; (b) *i.* NIS, MeCN/H_2O; *ii.* EDC·HCl, DMAP, DIPEA, DCM, 70% over 2 steps (1:9 α:β) for **70**, 90% over 2 steps (1:5 α:β) for **76**; (c) Ac_2O, DMAP, pyr. 100 °C, quant.; (d) TIPDS-Cl_2, imidazole, pyr., 82%; (e) TESOTf, pyr., 88%; (f) *i.* $AgNO_3$, 2,6-lutidine, H_2O, THF; *ii.* EDC·HCl, DMAP, DIPEA, DCM, 66% over 2 steps from **77**, 55% over 2 steps from **78**; (g) cyclopropylacetylene, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, 62% for **81**, 88% for **82**.

Table 3 shows the glycosylation of *ortho*-alkynylbenzoates **79-82** to doxorubicinone acceptor **23** under PPh_3AuNTf_2 catalysis, towards the synthesis of fucosamine-doxorubicinones **71** and **72**. The yields were modest to good for all four donors, but the stereoselectivityies of the glycosylations were poor. It has earlier been shown in the context of preactivation glycosylations (Ph_2SO, Tf_2O, TTBP, -80 °C to -40 °C) that the stereochemical outcome of fucosazidylation is very dependent on the acceptor nucleophilicity and is much more likely to proceed through S_N2-like pathways than for the 2-deoxyglycosides in this Thesis.[17] Unfortunately, only minimal amounts of the desired α-glycosidic products **79** and **81** could be isolated. Deprotection of the azide under Staudinger conditions proved unsuccessful, as the intermediate iminophosporane underwent attack of the tertiary 9-hydroxyl function, finally leading to aromatization of the attached ring as earlier shown for aklavinone **40** (Chapter 3, Scheme 7).

Table 2. Glycosylation of fucosazide *ortho*-alkynylbenzoates **79-82** to doxorubicinone-acceptor **23**.



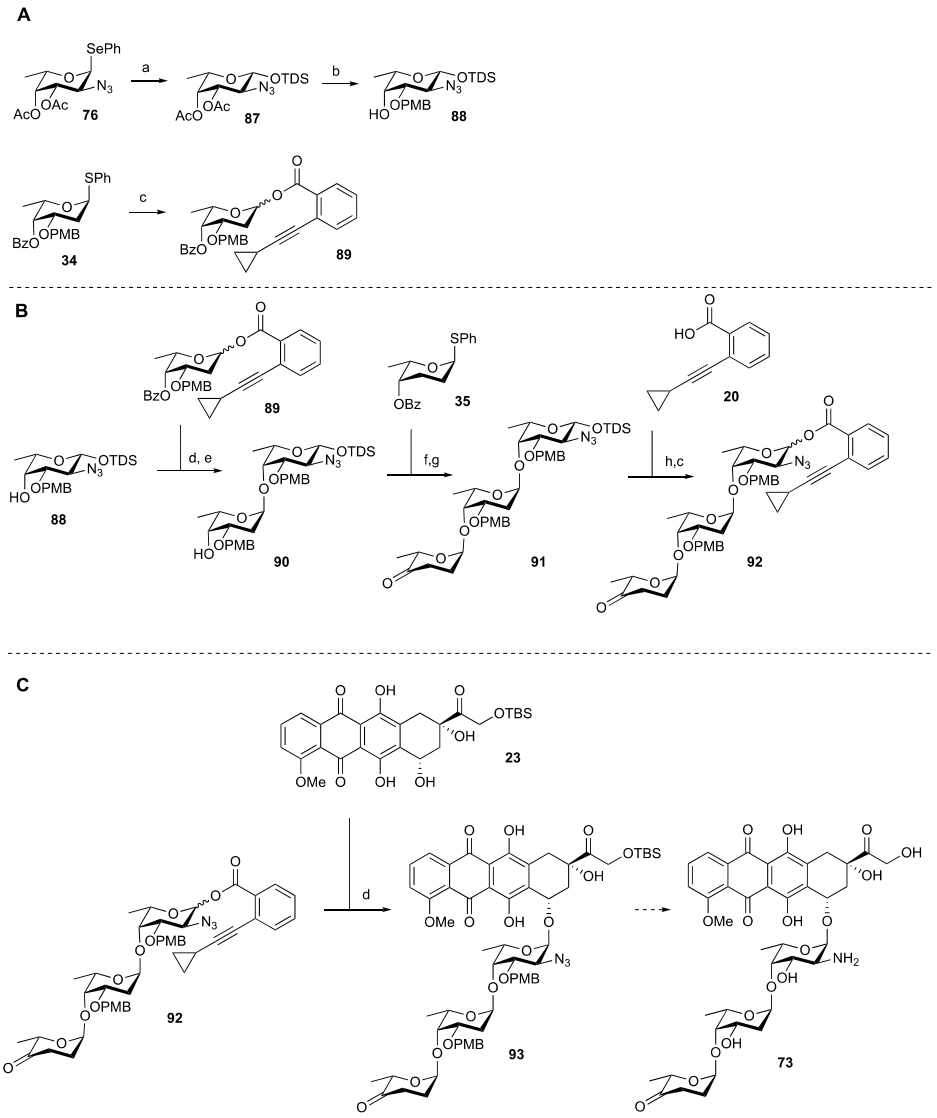
Reagents and conditions: (a) PPh_3AuNTf_2 (10 mol%), 0.05M in DCM.

Entry	Donor	Yield (α:β ratio)
1	 **79**	91% (3:1 α:β)
2	 **80**	52% (1.5:1 α:β)
3	 **81**	68% (2.6:1 α:β)
4	 **82**	67% (2.2:1 α:β)

The use of the tin(II)-thiophenolate conditions developed by Romea *et al*., successfully applied by the group of Roush in their total synthesis of spinosyn A, might circumvent this issue.[18,19]

Progress in the synthesis of fucosamine-trisaccharide doxorubicinone **68** is depicted in Scheme 8. Fucosazide acceptor **83** (Scheme 8A) was prepared by hydrolysis of selenoglycoside **71**, followed by installation of an anomeric dimethylthexyl silyl ether

(TDS) to furnish **82**. Deacylation providing the diol, followed by installation of a 3-PMB group through the stannylene acetal gave acceptor **83**. As appendage of the oliosyl moiety on this alcohol using thioglycoside **30** proved to be low-yielding (using IDCP) or aselective (2.2:1 α:β using NIS, TfOH, -78 °C to -40 °C), alkynylbenzoate **84** was prepared instead. Subjection of a mixture of fucosazide acceptor **83** and olioside **84** to catalytic PPh_3AuNTf_2 (-78 °C to RT) gave the desired disaccharide **85** in good yield after removal of the 4'-benzoate. Subjection to rhodinoside **35** in the presence of IDCP gave the desired trisaccharide stereoselectively. Removal of the terminal benzoate and oxidation of the resultant alcohol, using Dess-Martin periodinane furnished the terminal cineruloside **86**. Removal of the reducing end TDS ether was accomplished using HF·pyr complex, after which the resultant hemiacetal was subjected to Steglich esterification to *ortho*-cyclopropylethynylbenzoic acid **20**, giving trisaccharide donor **87**. Glycosylation of this donor to doxorubicinone-acceptor **55** under the agency of PPh_3AuNTf_2 proceeded in moderate yield and stereoselectivity to give a mixture from which α,α,α-trisaccharide **88** could be isolated. Deprotections to obtain **73** remain to be done upon successful deprotection of the azide towards the monosaccharidic fucosamines.



Scheme 8. Towards the synthesis of 2-fucosamine-trisaccharide **73**. *Reagents and conditions:* (a) *i.* NIS, MeCN, H_2O; *ii.* TDS-Cl, imidazole, DCM, 94% over 2 steps; (b) *i.* NaOMe, MeOH; *ii.* Bu_2SnO, toluene, 105 °C, then PMB-Cl, TBABr, toluene, 90 °C, 92% over 2 steps; (c) *i.* NIS, MeCN, H_2O; *ii.* EDC·HCl, DMAP, DIPEA, DCM, 84% over 2 steps (1:2.5 α:β) for **89**, 48% (1:1.5 α:β) for **92**; (d) PPh_3AuNTf_2, DCM, -78 °C to RT, 84% (14:1 α:β) for **90**, 47% (>7.7:1 α:β) for **93**; (e) NaOMe, MeOH, DCM, 63% for **90**, 80% for **91**; (f) *i.* IDCP, Et_2O,DCE; *ii.* NaOMe, MeOH, 80% over 2 steps; (g) Dess-Martin periodinane, $NaHCO_3$, DCM, 80%; (h) HF·pyr., THF, pyr., 92%.

Experimental procedures and characterization data

All reagents were of commercial grade and used as received. Traces of water from reagents were removed by co-evaporation with toluene in reactions that required anhydrous conditions. All moisture/oxygen sensitive reactions were performed under an argon atmosphere. DCM used in the glycosylation reactions was dried with flamed 4Å molecular sieves before being used. Reactions were monitored by TLC analysis with detection by UV (254 nm) and where applicable by spraying with 20% sulfuric acid in EtOH or with a solution of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4\cdot 2H_2O$ (10 g/L) in 10% sulfuric acid (aq.) followed by charring at ~150 °C. Flash column chromatography was performed on silica gel (40-63μm). ^1H and ^{13}C spectra were recorded on a Bruker AV 400 and Bruker AV 500 in $CDCl_3$, CD_3OD, pyridine-*d*5 or D_2O. Chemical shifts (δ) are given in ppm relative to tetramethylsilane (TMS) as internal standard (^1H NMR in $CDCl_3$) or the residual signal of the deuterated solvent. Coupling constants (J) are given in Hz. All ^{13}C spectra are proton decoupled. Column chromatography was carried out using silica gel (0.040-0.063 mm). Size-exclusion chromatography was carried out using Sephadex LH-20, using DCM:MeOH (1:1, v/v) as the eluent. Neutral silica was prepared by stirring regular silica gel in aqueous ammonia, followed by filtration, washing with water and heating at 150°C overnight. High-resolution mass spectrometry (HRMS) analysis was performed with a LTQ Orbitrap mass spectrometer (Thermo Finnigan), equipped with an electronspray ion source in positive mode (source voltage 3.5 kV, sheath gas flow 10 mL/min, capillary temperature 250 °C) with resolution R = 60000 at m/z 400 (mass range m/z = 150 – 2000) and dioctyl phthalate (m/z = 391.28428) as a "lock mass", or with a Synapt G2-Si (Waters), equipped with an electronspray ion source in positive mode (ESI-TOF), injection via NanoEquity system (Waters), with LeuEnk (m/z = 556.2771) as "lock mass". Eluents used: MeCN:H_2O (1:1 v/v) supplemented with 0.1% formic acid. The high-resolution mass spectrometers were calibrated prior to measurements with a calibration mixture (Thermo Finnigan).

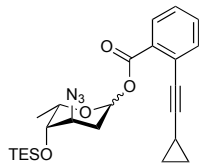
General procedure A: Silver-mediated hydrolysis of selenoglycosides
To a solution of thioglycoside or selenoglycoside in THF/H_2O (10:1 v/v, 0.16M) were added 2,6-lutidine (3 eq.) and $AgNO_3$ (3.5 eq.) and the reaction mixture was stirred overnight in the dark under regular atmosphere. Ethyl acetate and Na_2SO_4 were added and the reaction mixture was stirred for 1 h, filtered over Celite and concentrated *in vacuo* to give the crude hemiacetals.

General procedure B: Esterification with alkynylbenzoic acid or 2-iodobenzoic acid
To the hemi-acetal in DCM (0.1 M) were added DIPEA (9 eq), DMAP (1 eq), EDCI·HCl (3 eq) and freshly saponified *ortho*-cyclopropylethynylbenzoic acid (**20**) (3 eq) or 2-iodobenzoic (1.5 eq). After disappearance of the starting hemiacetal, the mixture was diluted with DCM and washed with sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography gave the corresponding anomeric benzoates.

General procedure C: *O*-glycosylations of alkynylbenzoate donors
To a solution of the alkynylbenzoate donor and 14-*O*-tert-butyldimethylsilyl-doxorubicinone **23** (1.5 eq) in DCM (0.05M), were added activated molecular sieves (4Å) and the mixture was stirred for 30 minutes. Subsequently, a freshly prepared 0.1M DCM solution of PPh_3AuNTf_2 (prepared by stirring 1:1 PPh_3AuCl and $AgNTf_2$ in DCM for 30 minutes) (1 mL/mmol, 0.1 eq) in DCM was added dropwise. After stirring 30 minutes, the mixture was filtered and concentrated *in vacuo*. Column chromatography gave the anthracycline glycosides.

General procedure D: *C*-glycosylations using allyltrimethylsilane: To solution of donor (1 eq) and allyltrimethylsilane (8 eq) in DCM (0.05 M) were added 4Å MS and the reaction mixture was stirred for 30 minutes. Subsequently, a freshly prepared 0.1M DCM solution of PPh_3AuNTf_2 (prepared by stirring 1:1 PPh_3AuCl and $AgNTf_2$ in DCM for 30 minutes) (0.1 eq) in DCM was added dropwise. After stirring for 30 minutes, the mixture was filtered and concentrated *in vacuo*. Column chromatography (1:99 Et_2O:pentane) afforded the *C*-glycosides. Flamedried molecular sieves contained too little water and gave rise to glycal formation, fresh molecular sieves shortly exposed to air (ca. 30 seconds) allowed formation of the desired products.

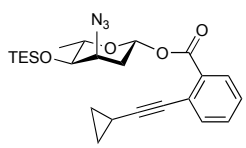
***o*-Cyclopropylethynylbenzoyl-3-*epi*-azido-2,3-dideoxy-4-triethylsilyl-L-fucopyranoside (57)**



Alcohol **24** (Chapter 5) (838 mg, 3.00 mmol) was dissolved in pyridine (10 mL), to which TESOTf (1.5 ml, 6.8 mmol, 2.2 eq) was added at 0 °C. After stirring for 1 h, Et_2O was added and the reaction mixture was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (5:95 EtOAc:pentane) afforded the silyl ether as a colorless oil (999 mg, 2.54 mmol, 85%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.08 – 6.91 (m, 2H), 6.88 – 6.76 (m, 2H), 5.46 (dd, *J* = 4.4, 1.9 Hz, 1H), 4.24 (qd, *J* = 6.6, 1.6 Hz, 1H), 3.42 – 3.27 (m, 1H), 2.38 (dt, *J* = 14.8, 4.2 Hz, 1H), 2.04 (dddd, *J* = 14.5, 3.2, 1.9, 0.9 Hz, 1H), 1.15 (d, *J* = 6.6 Hz, 3H), 0.99 (t, *J* = 7.9 Hz, 10H), 0.65 (q, *J* = 7.7 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7, 151.3, 117.6, 114.6, 95.0, 69.9, 63.8, 57.9, 55.8, 27.5, 16.7, 7.0, 4.9. HRMS: [M +Na]$^+$ calculated for $C_{19}H_{31}N_3O_4SiNa$ 416.19760; found 416.19757.

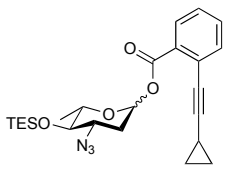
The above glycoside (394 mg, 1.0 mmol) was hydrolysed according to general procedure A. Column chromatography (5:95 – 10:90 EtOAc:pentane) afforded the corresponding hemi-acetal. This hemi-acetal was esterified with cyclopropylethynyl benzoic acid **20** (559 mg, 3.00 mmol, 3 eq) according to general procedure B. Column chromatography 2:98 Et_2O:pentane afforded the title compound as a colorless oil (286 mg, 0,628 mmol, 63%, 1:3 α:β). Spectral data for the β -anomer: ^{1}H NMR (400 MHz, Chloroform-*d*): δ 7.50 – 7.45 (m, 1H), 7.44 – 7.38 (m, 1 H), 7.34 – 7.27 (m, 1H), 6.23 (dd, J = 6.9, 2.8 Hz, 1H), 4.10 (qd, J = 6.7, 3.1 Hz, 1H), 4.00 (td, J = 6.0, 3.9 Hz, 1H), 3.56 (dd, J = 5.6, 3.1 Hz, 1H), 2.29 (ddd, J = 13.6, 6.9, 3.9 Hz, 1H), 1.91 (ddd, J = 13.6, 6.4, 2.9 Hz, 1H), 1.52 (tt, J = 6.8, 5.5 Hz, 1H), 1.29 (d, J = 6.7 Hz, 3H) , 1.00 (t, J = 7.9 Hz, 9H), 0.92-0.88 (m, 2H), 0.73-0.58 (m, 6H); ^{13}C NMR (100 MHz, Chloroform-*d*): δ 164.6, 134.5, 132.0, 130.8, 130.4, 127.1, 125.4, 114.6, 101.5, 99.7, 91.8, 74.7, 71.9, 70.6, 59.7, 31.4, 16.8, 9.0, 7.0, 4.6, 0.9. HRMS: [M + H$^+$] calculated for $C_{24}H_{34}N_3O_4Si$ 456.23131; found 456.23112.

***o*-Cyclopropylethynylbenzoyl-4-*O*-triethylsilyl-2,3,6-trideoxy-3-azido-β-L-ribohexapyranoside (58)**



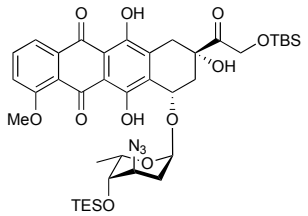
Glycoside **33** (Chapter 5) (797 mg, 2.00 mmol) was hydrolysed according to general procedure A. Column chromatography (5:95 – 10:90 EtOAc:pentane) afforded the hemi-acetal. The hemi-acetal was esterified with *ortho*-cyclopropylethynyl benzoic acid **20** (1.12 mg, 3.0 mmol, 3 eq) according to general procedure B. Column chromatography (3:97 Et_2O:pentane) afforded the title compound as a colorless oil (453 mg, 0.950 mmol, 49%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.91 (dd, *J* = 7.9, 1.4 Hz, 1H, Ar), 7.47 (dd, *J* = 7.8, 1.4 Hz, 1H, , Ar), 7.41 (td, *J* = 7.5, 1.4 Hz, 1H, Ar), 7.30 – 7.25 (m, 1H, Ar), 6.19 (dd, *J* = 8.8, 2.4 Hz, 1H, H-1), 4.12 – 3.95 (m, 2H, H-3, H-5), 3.64 (dd, *J* = 8.2, 3.2 Hz, 1H, H-4), 2.21 (ddd, *J* = 13.4, 4.5, 2.5 Hz, 1H, H-2$_{eq}$), 1.97 (ddd, *J* = 13.4, 8.8, 3.3 Hz, 1H, H-2$_{ax}$), 1.57 – 1.45 (m, 1H, C-propyl -CH-), 1.29 (d, *J* = 6.4 Hz, 3H, H-6), 1.01 (t, *J* = 7.9 Hz, 9H, TES -CH_3), 0.93 – 0.85 (m, 4H, C-propyl -CH_2-), 0.68 (qd, *J* = 8.3, 7.9, 1.6 Hz, 6H, TES -CH_2-). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.31 (C=O), 134.4 (Ar), 132.0 (Ar), 131.0 (Ar), 130.7 (Ar), 127.0 (Ar), 125.1 (Ar), 99.7 (-C≡C-), 91.4 (C-1), 74.6 (C-4), 74.5 (-C≡C-), 72.0 (C-5), 60.0 (C-3), 34.3 (C-2), 18.5 (C-6), 9.0 (C-propyl -CH_2-) 9.0 (C-propyl -CH_2), 7.0 (TES -CH_3), 5.0 (TES -CH_2), 0.8 (C-propyl -CH-). IR (thin film, cm^{-1}): 2956, 2938, 2912, 2231, 2098 (N_3), 1728, 1597, 1279, 1239, 1065. HRMS: [M+Na]$^+$ calculated for $C_{24}H_{33}N_3O_4SiNa$ 478.2133Na found 478.2133.

***o*-Cyclopropylethynylbenzoyl-3-azido-2,3-dideoxy-4-triethylsilyl-L-rhamnopyranoside (59)**



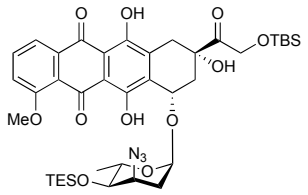
Glycoside **14** (Chapter 5) (862 mg, 2.19 mmol) was hydrolysed according to general procedure A. The crude hemi-acetal was esterified with *ortho*-cyclopropylethynyl benzoic acid **20** (1.22 g, 6.57 mmol, 3 eq) according to general procedure B. Column chromatography (3:97 Et_2O:pentane) afforded the title compound as a pale-yellow oil (614 mg, 1.30 mmol, 59%, 1:4 α:β). Spectral data for the β-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.97 (dd, J = 7.9, 1.4 Hz, 1H), 7.51 (dd, J = 7.8, 1.4 Hz, 1H), 7.46 (td, J = 7.6, 1.4 Hz, 1H), 7.32 (ddd, J = 7.9, 7.3, 1.5 Hz, 1H), 6.01 (dd, J = 9.9, 2.3 Hz, 1H), 3.56 – 3.50 (app m, 1H), 3.50 – 3.46 (app m, 1H), 3.20 (t, J = 9.0 Hz, 1H), 2.48 (ddd, J = 12.5, 4.9, 2.2 Hz, 1H), 1.94 (td, J = 12.5, 10.0 Hz, 1H), 1.55 (tt, J = 7.5, 5.5 Hz, 1H), 1.36 (d, J = 6.2 Hz, 3H), 1.03 (t, J = 7.9 Hz, 9H), 0.94 – 0.90 (m, 4H), 0.73 (qd, J = 8.3, 7.9, 2.8 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 164.2, 134.3, 132.1, 130.7, 130.5, 127.0, 125.1, 99.8, 92.2, 75.7, 74.5, 63.3, 35.4, 18.2, 8.9, 6.9, 5.2, 0.7. HRMS: [M+Na]$^+$ calculated for $C_{24}H_{33}N_3O_4SiNa$ 478.2133; found 478.2139.

7-[3-*epi*-Azido-2,3-dideoxy-4-triethylsilyl-L-fucopyranoside]-14-*O*-tert-butyldimethylsilyl-doxorubicinone (62)



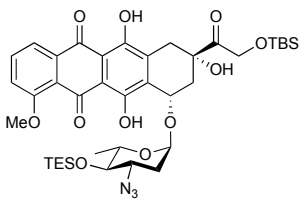
According to general procedure C, glycosyl donor **57** (50 mg, 0.11 mmol) was coupled to 14-*O*-*tert*-butyldimethylsilyl-doxorubicinone **23** (90 mg, 0.17 mmol 1.5 eq). Column chromatography (5:95 Et_2O:pentane - 2:98 – 20:80 acetone:toluene) afforded the title compound as a red solid (70 mg, 90 μmol, 84%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.92 (s, 1H), 13.24 (s, 1H), 8.05 – 7.97 (m, 1H), 7.76 (t, *J* = 8.1 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 5.43 (d, *J* = 4.0 Hz, 1H), 5.21 (dd, *J* = 3.9, 2.2 Hz, 1H), 5.10 (s, 1H), 5.05 – 4.86 (m, 2H), 4.30 – 4.12 (m, 1H), 4.09 (s, 3H), 3.68 (q, *J* = 3.7 Hz, 1H), 3.54 – 3.47 (m, 1H), 3.19 (dd, *J* = 19.0, 1.9 Hz, 1H), 2.98 (d, *J* = 18.9 Hz, 1H), 2.34 (dt, *J* = 14.9, 2.2 Hz, 1H), 2.28 – 2.10 (m, 2H), 1.78 – 1.68 (m, 1H), 1.35 – 1.18 (m, 7H), 1.07 – 0.91 (m, 21H), 0.66 (q, *J* = 7.9 Hz, 7H), 0.15 (d, *J* = 5.2 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.2, 187.2, 186.7, 161.1, 156.5, 156.1, 135.8, 134.5, 134.3, 134.2, 132.1, 129.4, 129.3, 121.0, 119.9, 118.4, 111.5, 111.3, 99.3, 77.1, 69.4, 66.9, 63.6, 58.8, 56.8, 35.7, 34.1, 28.0, 26.0, 16.8, 7.0, 4.9, -5.1, -5.3. HRMS: $[M+Na]^+$ calculated for $C_{39}H_{55}N_3O_{11}Si_3Na$ 820.32737; found 820.3266.

7-[3-*epi*-Azido-2,3-dideoxy-4-triethylsilyl-L-rhamnopyranoside]-14-*O*-tert-butyldimethylsilyl-doxorubicinone (63)



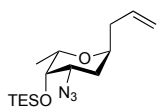
According to general procedure B glycosyl donor **58** (46 mg, 0.10 mmol) was coupled to 14-*O*-*tert*-butyldimethylsilyl-doxorubicinone **23** (79 mg, 0.15 mmol 1.5 eq). Column chromatography (1:9 Et_2O:pentane, then 5:95 – 10:90 acetone:toluene) afforded the title compound as a red solid (62 mg, 78 μmol, 78%, 3:1 α:β). Spectral data for the α-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.90 (s, 1H), 13.18 (s, 1H), 7.97 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.74 (dd, *J* = 8.4, 7.7 Hz, 1H), 7.37 (dd, *J* = 8.6, 1.1 Hz, 1H), 5.44 (s, 1H), 5.35 (d, *J* = 4.3 Hz, 1H), 5.20 (dd, *J* = 3.7, 2.2 Hz, 1H), 5.13 – 4.81 (m, 2H), 4.15 (dq, *J* = 9.1, 6.3 Hz, 1H), 4.08 (s, 3H), 3.82 (q, *J* = 3.4 Hz, 1H), 3.57 (dd, *J* = 9.2, 3.1 Hz, 1H), 3.15 (dd, *J* = 18.9, 1.9 Hz, 1H), 2.91 (d, *J* = 18.9 Hz, 1H), 2.30 (dt, *J* = 14.7, 2.2 Hz, 1H), 2.13 (dd, *J* = 14.7, 3.8 Hz, 1H), 2.01 – 1.91 (m, 1H), 1.86 (dt, *J* = 14.9, 4.2 Hz, 1H), 1.29 (d, *J* = 6.3 Hz, 3H), 1.03 – 0.95 (m, 18H), 0.68 (qd, *J* = 8.3, 7.9, 2.3 Hz, 6H), 0.16 (d, *J* = 2.0 Hz, 6H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 212.6, 187.1, 186.6, 161.0, 156.4, 156.1, 135., 135.6, 134.7, 134.4, 120.9, 119.9, 118.4, 111.4, 111.2, 98.1, 76.9, 74.8, 68.4, 66.8, 65.5, 59.5, 56.8, 35.7, 34.0, 26.0, 18.0, 7.0, 5.0, -5.2, -5.3. HRMS: $[M+Na]^+$ calculated for $C_{24}H_{33}N_3O_4SiNa$ 478.21325; found 478.2133.

7-[4-*epi*-Azido-2,3-dideoxy-4-triethylsilyl-L-fucopyranoside]-14-*O*-tert-butyldimethylsilyl-doxorubicinone (64)



According to general procedure C, glycosyl donor **59** (78 mg, 0.17 mmol) was coupled to 14-*O*-*tert*-butyldimethylsilyl-doxorubicinone **23** (132 mg, 0.250 mmol 1.5 eq). Column chromatography (4:96 Et_2O:pentane, then 1:199 acetone:toluene) and size-exclusion chromatography (Sephadex LH-20, eluent: 1:1 v/v DCM:MeOH) afforded the title compound as a red solid (120 mg, 0.15 mmol, 91%, 3:1 α:β). Spectal data for the α-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.99 (s, 1H), 13.21 (s, 1H), 8.03 (d, *J* = 7.6 Hz, 1H), 7.80 (t, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 5.48 (d, *J* = 3.9 Hz, 1H), 5.25 (dd, *J* = 4.2, 2.1 Hz, 1H), 5.03 – 4.85 (m, 2H), 4.50 (s, 1H), 4.11 (s, 3H), 3.79 (dq, *J* = 9.0, 6.3 Hz, 1H), 3.45 (ddd, *J* = 12.4, 9.1, 4.8 Hz, 1H), 3.17 (t, *J* = 17.7 Hz, 1H), 2.93 (d, *J* = 18.8 Hz, 1H), 2.35 (dt, *J* = 14.9, 2.1 Hz, 1H), 2.26 – 2.15 (m, 2H), 1.77 (td, *J* = 13.5, 4.1 Hz, 1H), 1.32 (d, *J* = 6.2 Hz, 3H), 1.01 (t, *J* = 7.9 Hz, 9H), 0.99 (s, 9H), 0.71 (qd, *J* = 8.3, 7.9, 2.5 Hz, 6H), 0.17 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.3, 187.0, 186.6, 161.0, 156.3, 155.7, 135.8, 135.4, 134.2, 133.6, 120.7, 119.8, 118.5, 111.4, 111.3, 100.1, 76.2, 70.1, 66.7, 61.2, 56.7, 35.7, 35.4, 33.8, 29.7, 25.9, 18.6, 18.1, 6.9, 5.2, -5.4, -5.4. HRMS: $[M + Na]^+$ calculated for $C_{39}H_{55}N_3O_{11}Si_2Na$ 820.3267; found 820.3279.

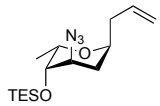
3-(3'-Azido-2',3'-dideoxy-4'-*O*-triethylsilyl-α-L-fucopyranosyl)-1-propene (65)



According to general procedure D, the title compound was obtained from glycosyl donor **56** as a colorless oil (22 mg, 71 μmol, 71%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.78 (ddt, *J* = 17.2, 10.2, 6.9 Hz, 1H), 5.17 – 5.00 (m, 2H), 3.98 – 3.89 (m, 2H), 3.85 (tdd, *J* = 7.2, 5.6, 2.0 Hz, 2H), 2.28 (dtt, *J* = 14.1, 6.9, 1.4 Hz, 1H), 2.16 (dddt, *J* = 14.3, 7.2, 6.0, 1.3 Hz, 1H), 1.83 (ddd, *J*

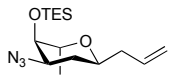
= 13.7, 5.3, 2.9 Hz, 1H), 1.52 (ddd, *J* = 13.7, 9.2, 3.6 Hz, 1H), 1.39 (d, *J* = 6.6 Hz, 3H), 0.98 (t, *J* = 7.9 Hz, 9H), 0.64 (td, *J* = 8.0, 7.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.7, 117.2, 71.9, 71.1, 64.7, 59.7, 38.9, 33.6, 14.2, 7.0, 4.9.

3-(3'-Azido-2',3'-dideoxy-4'-*O*-triethylsilyl-α-L-xylopyranosyl)-1-propene (66)



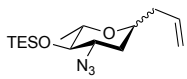
According to general procedure D, the title compound was obtained from glycosyl donor **57** as a colorless oil (27 mg, 87 μmol, 87%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.77 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.16 – 5.01 (m, 2H), 4.09 (qd, *J* = 6.9, 5.5 Hz, 1H), 3.71 (dtd, *J* = 12.1, 6.3, 2.3 Hz, 1H), 3.64 (dd, *J* = 9.6, 5.7 Hz, 1H), 3.56 (ddd, *J* = 11.9, 9.6, 4.7 Hz, 1H), 2.26 (dtt, *J* = 13.6, 6.8, 1.3 Hz, 1H), 2.17 (dddt, *J* = 14.2, 7.1, 5.8, 1.4 Hz, 1H), 1.95 (ddd, *J* = 13.1, 4.7, 2.3 Hz, 1H), 1.33 – 1.25 (m, 1H), 1.23 (d, *J* = 6.9 Hz, 3H), 0.98 (t, *J* = 7.9 Hz, 9H), 0.73 – 0.57 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.33, 117.44, 73.80, 73.01, 67.09, 60.39, 40.17, 36.59, 11.81, 6.86, 4.94. HRMS: $[M-N_2+H]^+$ calculated for $C_{15}H_{30}NO_2Si$: 284.2040; found 284.2046.

3-(3'-Azido-2',3'-dideoxy-4'-*O*-triethylsilyl-α-L-ribohexopyranosyl)-1-propene (67)



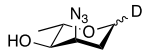
According to general procedure D, the title compound was obtained from glycosyl donor **58** as a colorless oil (22 mg, 74 μmol 74%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.81 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.16 – 5.02 (m, 2H), 3.99 (qd, *J* = 6.9, 3.6 Hz, 1H), 3.73 (dtd, *J* = 8.6, 6.5, 3.4 Hz, 1H), 3.64 (t, *J* = 3.2 Hz, 1H), 3.50 – 3.42 (m, 1H), 2.47 (dtt, *J* = 13.8, 6.8, 1.4 Hz, 1H), 2.34 – 2.23 (m, 1H), 1.94 (ddd, *J* = 12.8, 10.1, 8.7 Hz, 1H), 1.74 (dt, *J* = 12.7, 3.8 Hz, 1H), 1.19 (d, *J* = 6.9 Hz, 3H), 0.99 (t, *J* = 7.9 Hz, 9H), 0.71 – 0.62 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.75, 117.30, 72.73, 72.69, 69.00, 57.33, 39.59, 30.21, 16.32, 6.93, 5.06. HRMS: $[M-N_2+H]^+$ calculated for $C_{15}H_{30}NO_2Si$: 284.2040; found 284.2047.

3-(3'-Azido-2',3'-dideoxy-4'-*O*-triethylsilyl-α-β-L-rhamnopyranosyl)-1-propene (68)



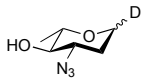
According to general procedure D, the title compound was obtained from glycosyl donor **59** as a colorless oil (25 mg, 60 μmol, 60%). Spectral data for the α-anomer: ^{1}H NMR (600 MHz, Chloroform-*d*) δ 5.81 – 5.71 (m, 1H), 5.16 – 5.05 (m, 2H), 4.02 – 3.95 (m, 1H), 3.84 – 3.74 (m, 1H), 3.54 – 3.45 (m, 2H), 3.09 (t, *J* = 8.6 Hz, 1H), 2.59 – 2.51 (m, 1H), 2.31 – 2.23 (m, 1H), 2.00 (dddd, *J* = 13.4, 4.8, 2.1, 0.5 Hz, 1H), 1.82 (ddd, *J* = 13.4, 11.7, 5.8 Hz, 1H), 1.22 (d, *J* = 6.2 Hz, 3H), 0.99 (t, *J* = 7.9 Hz, 13H), 0.72 – 0.65 (m, 8H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 134.5, 117.5, 76.6, 71.3, 70.1, 62.0, 35.7, 32.9, 18.7, 7.0, 5.4.

1-Deutero-2,3-dideoxy-3-azido-L-ribohexapyranoside (69)



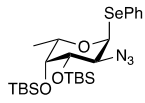
To a solution of donor **58** (46 mg, 0.1 mmol) in DCM (2 mL) were added TES-D (127 μL, 94 mg, 0.8 mmol 8 eq) and 4 Å MS. A freshly prepared 0.1M DCM solution of PPh_3AuNTf_2 (prepared by stirring 1:1 PPh_3AuCl and $AgNTf_2$ in DCM for 30 minutes) (100 μL 0.01 mmol, 0.1 eq) and the reaction mixture was stirred for 1h, filtered and concentrated *in vacuo*. Column chromatography (0:100 – 30:70 Et_2O:pentane) afforded the title compound as a colourless oil (13 mg, 83 μmol, 83%, 93:7 α:β). Spectal data for the α-anomer: ^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.10 (q, *J* = 3.4 Hz, 1H), 3.74 – 3.70 (m, 0.93H,), 3.51 (dq, *J* = 9.1, 6.2 Hz, 1H), 3.34 (td, *J* = 9.2, 3.6 Hz, 1H), 2.04 – 1.87 (m, 3H), 1.27 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ 73.2, 73.0, 61.7, 61.6, 61.4, 61.1, 30.2, 18.1. ^{2}H NMR (77 MHz, Chloroform-*d*) δ 3.65 (D-1α).

1-Deutero-2,3-dideoxy-3-azido-L-rhamnopyranoside (70)



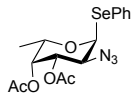
To a solution of donor **59** (46 mg, 0.1 mmol) in DCM (2 mL) were added TES-D (127 μL, 94 mg, 0.8 mmol 8 eq) and 4 Å MS. A freshly prepared 0.1M DCM solution of PPh_3AuNTf_2 (prepared by stirring 1:1 PPh_3AuCl and $AgNTf_2$ in DCM for 30 minutes) (100 μL 0.01 mmol, 0.1 eq) and the reaction mixture was stirred for 1h. More PPh_3AuNTf_2 was added (in 1.1 mL DCM, 0.11 mmol, 1.1 eq) and the reaction mixture was stirred for another 1 h, filtered and concentrated *in vacuo*. Column chromatography (0:100 – 50:50 Et_2O:pentane) afforded the title compound as a colorless oil (12 mg, 78 μmol, 78%, >10:1 α:β). Spectal data for the α-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.97 (dq, *J* = 5.1, 1.7 Hz, 1H), 3.46 – 3.38 (m, 1H), 3.27 (dq, *J* = 9.0, 6.1 Hz, 1H), 3.15 (t, *J* = 9.1 Hz, 1H), 2.02 (ddd, *J* = 13.1, 4.9, 1.8 Hz, 1H), 1.85 – 1.72 (m, 1H), 1.33 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 76.6, 76.1, 65.6, 65.5, 65.4, 65.3, 65.1, 65.1, 64.4, 30.9, 18.2.

Phenyl 2-azido-3,4-di-*O*-*tert*-butyldimethylsilyl-2-deoxy-seleno-α-L-fucopyranoside (75)



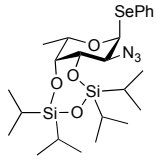
To an ice-cooled solution of diol **74**[17] (690 mg, 2.10 mmol) in DMF (4 mL) and pyridine (1.05 mL, 12.9 mmol, 6.15 eq), *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.44 mL, 6.29 mmol, 3.00 eq) was added dropwise. After stirring for 3 days while warming up to ambient temperature, the resulting solution was quenched with sat. aq. $NaHCO_3$ and the aqueous layer extracted five times with Et_2O. The combined organic layers were concentrated *in vacuo*, subsequently partitioned between Et_2O and H_2O and the organic layer successively washed four times with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (3:97 – 10:90 toluene:pentane) afforded the title compound as a colorless oil (1.17 g, 2.10 mmol, quant.). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.66 – 7.61 (m, 2H), 7.33 – 7.27 (m, 3H), 5.99 (d, *J* = 4.9 Hz, 1H), 4.28 (q, *J* = 6.5 Hz, 1H), 4.18 (dd, *J* = 10.1, 5.0 Hz, 1H), 3.88 (dd, *J* = 10.2, 2.2 Hz, 1H), 3.80 (d, *J* = 2.2 Hz, 1H), 1.20 (d, *J* = 6.5 Hz, 3H), 1.04 (s, 9H), 0.98 (s, 9H), 0.27 (s, 3H), 0.24 (s, 3H), 0.23 (s, 3H), 0.15 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.8, 129.0, 128.8, 127.7, 86.0, 77.5, 77.2, 76.8, 74.7, 73.9, 70.4, 62.6, 29.8, 26.5, 26.2, 18.6, 17.2, -3.4, -3.8, -4.4, -4.4.

Phenyl 3,4-di-*O*-acetyl-2-azido-2-deoxy-seleno-α-L-fucopyranoside (76)



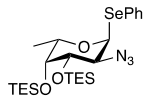
Diol **74** (1.68 g, 5.10 mmol) was dissolved in pyridine (25 mL) and acetic anhydride (40 mL), whereupon a catalytic amount of 4-dimethylaminopyridine was added. After heating to 100 °C and stirring for 1 hour, the resulting solution was diluted with DCM, quenched with sat. aq. $NaHCO_3$ and the aqueous layer extracted with DCM. The combined organic layers were then dried over $MgSO_4$ and concentrated *in vacuo* to afford the title compound as a viscous orange oil (2.10 g, 5.10 mmol, quant.). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.59 – 7.54 (m, 2H), 7.29 – 7.23 (m, 3H), 5.95 (d, *J* = 5.4 Hz, 1H), 5.31 (d, *J* = 3.3 Hz, 1H), 5.12 (dd, *J* = 10.9, 3.2 Hz, 1H), 4.47 (d, *J* = 6.4 Hz, 1H), 4.24 (dd, *J* = 10.8, 5.4 Hz, 1H), 2.15 (s, 3H), 2.04 (s, 3H), 1.06 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 169.4, 134.5, 129.0, 127.9, 127.8, 84.2, 77.5, 77.2, 76.8, 71.4, 69.9, 67.2, 58.5, 20.4, 20.4, 15.6. HRMS: $[M+H]^+$ calculated for $C_{16}H_{20}N_3O_5Se$ 412.3150; found 413.2546.

Phenyl-2-azido-3,4-*O*-tetraisopropyldisiloxane-2-deoxy-1-seleno-α-L-fucopyranoside (77)



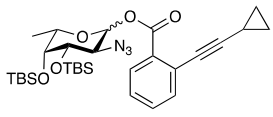
To a solution of diol **74** (328 mg, 1.00 mmol) in pyridine (5 mL) were added 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (0.36 mL, 0.35 mg, 1.1 mmol, 1.1 eq) and imidazole (136 mg, 2 mmol, 2 eq). After stirring for two days, Et_2O (100 mL) was added and the mixture was washed with 1M HCl, sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (0:100 – 5:95 Et_2O:pentane) afforded the title compound as a pale-yellow oil (470 mg, 0.820 mmol, 82%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.91 – 7.49 (m, 2H), 7.27 (dd, *J* = 5.2, 2.1 Hz, 3H), 5.87 (d, *J* = 5.2 Hz, 1H), 4.35 (dt, *J* = 7.1, 5.9 Hz, 1H), 4.19 – 4.11 (m, 2H), 4.04 (ddd, *J* = 10.9, 5.1, 1.3 Hz, 1H), 1.22 (d, *J* = 6.5 Hz, 3H), 1.17 – 0.92 (m, 28H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.5, 129.2, 129.0, 129.0, 127.8, 85.7, 75.9, 73.2, 69.2, 62.1, 17.8, 17.8, 17.5, 17.3, 17.3, 17.3, 17.2, 17.2, 16.8, 14.8, 13.6, 13.2, 12.8. HRMS: $[M - N_2 + H]^+$ calculated for $C_{24}H_{42}NO_4SeSi_2$ 544.1818; found 544.1813.

Phenyl-2-azido-3,4-*O*-di-triethylsilyl-2-deoxy-1-seleno-α-L-fucopyranoside (78)



To a solution of diol **74** (328 mg, 1.00 mmol) in pyridine (5 mL) was added triethylsilyl triflate (0.65 mL, 3 mmol, 3 eq). After stirring overnight Et_2O was added and the reaction mixture was washed with 1M HCl, sat. aq. $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (0:100 - 5:95 Et_2O:pentane) afforded the title compound as a pale-yellow oil (490 mg, 0.880 mmol, 88%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.71 – 7.50 (m, 2H), 7.34 – 7.12 (m, 3H), 5.93 (d, *J* = 5.1 Hz, 1H), 4.25 – 4.17 (m, 1H), 4.14 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.77 (dd, *J* = 10.1, 2.5 Hz, 1H), 3.73 (dd, *J* = 2.6, 1.0 Hz, 1H), 1.15 (d, *J* = 6.4 Hz, 3H), 1.01 (dt, *J* = 23.0, 7.9 Hz, 18H), 0.81 – 0.59 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.6, 129.1, 129.0, 127.7, 85.9, 74.7, 73.8, 70.2, 62.4, 16.8, 7.1, 5.4, 5.1.

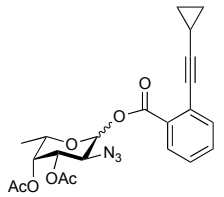
***o*-Cyclopropylethynylbenzoyl 2-azido-3,4-di-*O*-*tert*-butyldimethylsilyl-2-deoxy-α-L-fucopyranoside (79)**



To a solution of fucosyl selenide **75** (1.17 g, 2.10 mmol) in 10:1 MeCN:H_2O (38.5 mL, v/v) was added *N*-iodosuccinimide (590 mg, 2.62 mmol, 1.25 eq). After stirring for 1 hour, the resulting solution was diluted with EtOAc and successively washed with 10% aq. $Na_2S_2O_3$ and brine. The combined aqueous layers were then extracted with EtOAc and the resulting combined organic

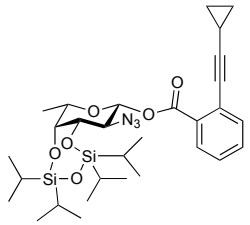
layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (3:97 – 20:80 toluene:pentane) afforded the intermediate lactol, a white crystalline solid, as a mixture of anomers (798 mg, 1.91 mmol, 91%, 1:2 α:β). The hemi-acetal was esterified with *ortho*-cyclopropylethynyl benzoic acid **20** according to general procedure B. Purification by column chromatography (1.5:98.5 – 2.5:97.5 EtOAc:pentane) afforded β-anomer (249 mg, 0.425 mmol, 22%) and an α:β anomeric mixture (619 mg, 1.06 mmol, 55%, 1:5 α:β), as colorless oils. Spectral data for the β anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.03 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.49 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.43 (td, *J* = 7.5, 1.4 Hz, 1H), 7.31 (td, *J* = 7.7, 1.5 Hz, 1H), 5.68 (d, *J* = 8.3 Hz, 1H), 3.84 (dd, *J* = 10.1, 8.3 Hz, 1H), 3.71 (q, *J* = 6.4 Hz, 1H), 3.67 (d, *J* = 2.4 Hz, 1H), 3.54 (dd, *J* = 10.1, 2.4 Hz, 1H), 1.53 (tt, *J* = 9.4, 5.2 Hz, 1H), 1.27 (d, *J* = 6.4 Hz, 3H), 0.96 (s, 18H), 0.90 (s, 2H), 0.89 (s, 2H), 0.19 (s, 3H), 0.18 (s, 3H), 0.15 (s, 3H), 0.11 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 134.5, 132.3, 130.9, 130.2, 127.1, 125.6, 100.1, 94.1, 77.5, 76.8, 74.8, 74.7, 74.0, 72.5, 63.5, 26.4, 26.3, 18.7, 18.6, 17.5, 9.1, 9.0, 0.9, -3.4, -3.5, -4.2, -4.4. HRMS: $[M+Na]^+$ calculated for $C_{30}H_{47}N_3O_5Si_2Na$ 6082952; found 608.2946.

***o*-Cyclopropylethynylbenzoyl 3,4-di-*O*-acetyl-2-azido-2-deoxy-L-fucopyranoside (80)**



To a solution of fucosyl selenide **76** (796 mg, 1.93 mmol) in 10:1 MeCN:H_2O (35.2 mL, v/v) was added *N*-iodosuccinimide (542 mg, 2.41 mmol, 1.25 eq). After stirring for 2 hours, the resulting solution was diluted with EtOAc and successively washed with 10% aq. $Na_2S_2O_3$ and brine. The combined aqueous layers were then extracted with EtOAc and the resulting combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (5:95 – 20:80 EtOAc:pentane) afforded the intermediate lactol, an orange wax, as a mixture of anomers (517 mg, 1.93 mmol, 98%, 1:1 α:β). The hemi-acetal was esterified with *ortho*-cyclopropylethynyl benzoic acid **20** according to general procedure B. Purification by column chromatography (2.5:97.5 – 33.3:66.7 EtOAc:pentane) afforded isolated α and β title benzoates **80α** (100 mg, 0.227 mmol, 15%) and **80β** (515 mg, 1.17 mmol, 77%), as slow crystallizing green oils. Spectral data for the α anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.97 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.52 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.46 (td, *J* = 7.5, 1.4 Hz, 1H), 7.35 (td, *J* = 7.6, 1.5 Hz, 1H), 6.59 (d, *J* = 3.7 Hz, 1H), 5.49 (dd, *J* = 11.0, 3.2 Hz, 1H), 5.41 (dd, *J* = 3.2, 1.3 Hz, 1H), 4.49 (q, *J* = 6.5 Hz, 1H), 4.07 (dd, *J* = 11.0, 3.7 Hz, 1H), 2.21 (s, 3H), 2.08 (s, 3H), 1.67 – 1.58 (m, 1H), 1.19 (d, *J* = 6.5 Hz, 3H), 0.97 – 0.87 (m, 3H), 0.86 – 0.79 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 169.9, 164.4, 135.1, 132.4, 131.0, 130.3, 127.4, 125.0, 99.9, 91.5, 77.5, 76.8, 74.9, 70.2, 69.9, 67.7, 57.2, 29.8, 20.8, 20.7, 16.1, 9.1, 9.0, 0.6. Spectral data for the β anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.02 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.52 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.46 (td, *J* = 7.5, 1.4 Hz, 1H), 7.32 (td, *J* = 7.6, 1.5 Hz, 1H), 5.85 (d, *J* = 8.5 Hz, 1H), 5.29 (d, *J* = 3.3 Hz, 1H), 5.06 (dd, *J* = 10.8, 3.4 Hz, 1H), 4.06 (q, *J* = 6.3 Hz, 1H), 3.98 (dd, *J* = 10.8, 8.5 Hz, 1H), 2.19 (s, 3H), 2.08 (s, 3H), 1.59 – 1.50 (m, 1H), 1.23 (d, *J* = 6.4 Hz, 3H), 0.93 (s, 2H), 0.91 (d, *J* = 3.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.0, 169.4, 163.3, 134.1, 132.2, 130.5, 129.5, 126.8, 125.2, 99.9, 93.0, 77.5, 76.8, 74.2, 71.6, 70.0, 69.2, 59.8, 20.3, 20.3, 15.7, 8.6, 0.5. HRMS: $[M+Na]^+$ calculated for $C_{22}H_{23}N_3O_7Na$ 441.1536; found 464.1428.

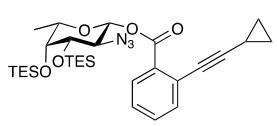
***o*-Cyclopropylethynylbenzoyl-2-azido-3,4-*O*-tetraisopropyldisiloxane-2-deoxy-β-L-fucopyranoside (81)**



Selenoglycoside **77** (470 mg, 0.820 mmol, 1 eq) was hydrolysed according to general procedure A. The resulting crude lactol was esterified with 2-iodobenzoic acid (305 mg, 1.23 mmol, 1.5 eq) according to general method B. Column chromatography (1:99 – 5:95 EtOAc:pentane) afforded the title compound as a white solid (289 mg, 55%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.02 (t, *J* = 8.5 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 5.61 (d, *J* = 8.6 Hz, 1H), 4.09 (d, *J* = 3.1 Hz, 1H), 4.04 (dd, *J* = 9.8, 3.1 Hz, 1H), 3.86 – 3.75 (m, 2H), 1.36 (d, *J* = 6.4 Hz, 3H), 1.19 – 1.02 (m, 28H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.0, 141.9, 133.5, 132.8, 132.0, 128.0, 95.1, 93.5, 77.2, 72.5, 71.8, 17.6, 17.6, 17.5, 17.2, 17.2, 17.0, 14.6, 13.5, 13.1, 12.6. HRMS $[M+Na]^+$ calculated for $C_{25}H_{40}IN_3O_6Si_2$: 684.1398, found 684.1390. To a solution of the above benzoate (289 mg, 0.45 mmol, 1 eq). in triethylamine (1.5 mL) and THF (1 mL) were added ethynyl cyclopropane (89 mg, 0.11 mL, 1.3 mmol, 3 eq), bis(triphenylphosphine)palladium dichloride (35 mg, 0.05 mmol, 0.1 eq and 10 mg) and copper iodide (0.05 mmol, 0.1 eq). The reaction mixture was stirred overnight, filtered over Celite and stirred for 1 hour with sat. aq. NH_4Cl. Pentane was added and the aqueous layer was extracted with 1% EtOAc in pentane.

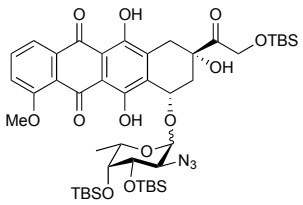
Combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (0:100 - 1:90 Et_2O in pentane) afforded the title compound as a yellow oil (231 mg 0.400 mmol, 88%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.02 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.49 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.43 (td, *J* = 7.5, 1.4 Hz, 1H), 7.31 (td, *J* = 7.6, 1.5 Hz, 1H), 5.63 (d, *J* = 8.6 Hz, 1H), 4.08 (dd, *J* = 3.2, 1.0 Hz, 1H), 4.02 (dd, *J* = 9.9, 3.1 Hz, 1H), 3.85 – 3.75 (m, 2H), 1.58 – 1.47 (m, 1H), 1.35 (d, *J* = 6.4 Hz, 3H), 1.10 (qd, *J* = 8.8, 5.7 Hz, 28H), 0.92 – 0.84 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 134.4, 132.3, 131.0, 130.3, 127.0, 125.5, 100.1, 93.2, 77.3, 74.6, 72.6, 71.7, 63.2, 17.7, 17.7, 17.5, 17.2, 17.2, 17.2, 17.0, 14.6, 13.5, 13.2, 12.7, 9.0, 0.8. HRMS: $[M+Na]^+$ calculated for $C_{30}H_{45}N_3O_6Si_2Na$ 622.27391; found 622.2744.

_o_-Cyclopropylethynylbenzoyl-2-azido-3,4-_O_-di-triethylsilyl-2-deoxy-β-L-fucopyranoside (82)



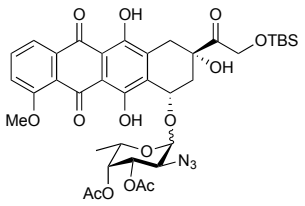
Selenoglycoside **78** (390 mg, 0.500 mmol) was hydrolysed according to general procedure A. The crude hemi-acetal was esterified with 2-iodobenzoic acid (186 mg, 0.750 mmol, 1.5 eq) according to general method B. Purification by column chromatography (2:98 – 5:95 EtOAc:pentane) afforded the title compound as a pale-yellow oil (200 mg, 0.330 mmol, 66%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 (ddd, *J* = 7.5, 5.8, 1.4 Hz, 2H), 7.43 (td, *J* = 7.6, 1.2 Hz, 1H), 7.18 (td, *J* = 7.6, 1.7 Hz, 1H), 5.62 (d, *J* = 8.4 Hz, 1H), 3.84 (dd, *J* = 10.0, 8.4 Hz, 1H), 3.73 – 3.59 (m, 2H), 3.53 (dd, *J* = 10.0, 2.6 Hz, 1H), 1.27 (d, *J* = 6.4 Hz, 3H), 1.00 (dt, *J* = 7.9, 4.4 Hz, 18H), 0.79 – 0.59 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 142.0, 133.5, 132.7, 132.0, 128.1, 95.2, 94.4, 74.6, 73.8, 72.5, 63.4, 17.0, 7.1, 5.3, 5.0. HRMS: $[M+Na]^+$ calculated for $C_{25}H_{42}IN_3O_5Si_2Na$ 670.1600; found 670.1612. To a solution of the above benzoate (193 mg, 0.320 mmol, 1 eq) in triethylamine (1 mL) were added cyclopropyl acetylene (80 µL, 0.96 mmol, 3 eq), bis (triphenylphosphine) palladium dichloride (21 mg, 0.03 mmol, 0.1 eq) and CuI (6 mg, 0.03 mmol, 0.1 eq). After stirring overnight sat aq. NH_4Cl was added and the resulting mixture was stirred for 1 hour. Pentane was added and the aqueous layer was extracted with 1% EtOAc in pentane. Combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (0:100 – 1:90 Et_2O:pentane) afforded the title product as a pale-yellow oil (100 mg, 0.180 mmol, 62%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.04 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.49 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.43 (td, *J* = 7.5, 1.4 Hz, 1H), 7.31 (td, *J* = 7.6, 1.5 Hz, 1H), 5.65 (d, *J* = 8.5 Hz, 1H), 3.83 (dd, *J* = 10.1, 8.4 Hz, 1H), 3.73 – 3.61 (m, 2H), 3.51 (dd, *J* = 10.1, 2.6 Hz, 1H), 1.52 (dt, *J* = 7.8, 5.8 Hz, 1H), 1.26 (d, *J* = 6.4 Hz, 3H), 1.00 (td, *J* = 8.0, 2.3 Hz, 18H), 0.92 – 0.87 (m, 4H), 0.79 – 0.61 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.2, 134.5, 132.4, 131.1, 130.2, 127.1, 125.7, 100.2, 94.1, 74.6, 73.9, 72.5, 63.5, 17.0, 9.0, 7.2, 7.0, 5.4, 5.1, 0.9. HRMS: $[M+H]^+$ calculated for $C_{30}H_{48}N_3O_5Si_2$ 586.3127; found 586.2771.

7-[2-Azido-3,4-di-_O_-tert-butyldimethylsilyl-2-deoxy-α-L-fucopyranoside]-14-_O_-_tert_-butyldimethylsilyl-doxorubicinone (83)



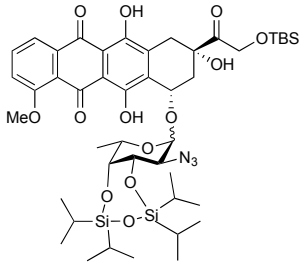
According to general procedure C, glycosyl donor **79** (114 mg, 0.195 mmol) was coupled to 14-*O*-TBS-doxorubicinone **23** (123 mg, 0.236 mmol, 1.2 eq). Purification by column chromatography (5:95 EtOAc:pentane then 1:399 acetone:toluene) afforded protected the title compound as a red amorphous solid (164 mg, 0.177 mmol, 91%, 3:1 α:β). Spectral data for the α anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.98 (s, 1H), 13.12 (s, 1H), 7.93 (d, *J* = 7.6 Hz, 1H), 7.71 (t, *J* = 8.1 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 5.57 (d, *J* = 2.7 Hz, 1H), 5.38 (t, *J* = 2.9 Hz, 1H), 4.94 (d, *J* = 20.0 Hz, 1H), 4.87 (d, *J* = 20.1 Hz, 1H), 4.58 (s, 1H), 4.06 (s, 3H), 3.98 (q, *J* = 6.5 Hz, 1H), 3.80 – 3.70 (m, 3H), 3.17 (d, *J* = 19.1 Hz, 1H), 2.93 (d, *J* = 19.0 Hz, 1H), 2.29 (d, *J* = 14.0 Hz, 1H), 2.23 – 2.18 (m, 1H), 1.27 (d, *J* = 6.6 Hz, 3H), 0.96 (s, 9H), 0.94 (s, 9H), 0.90 (s, 9H), 0.15 (br. s, 6H), 0.14 (s, 3H), 0.10 (s, 3H), 0.10 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.3, 186.8, 186.7, 161.0, 156.3, 155.6, 135.7, 135.4, 134.4, 133.3, 120.8, 119.7, 118.5, 111.6, 111.5, 99.3, 77.5, 77.3, 76.8, 74.9, 71.4, 69.4, 67.8, 66.6, 60.9, 56.8, 35.9, 34.5, 29.8, 26.3, 26.2, 26.0, 18.7, 18.7, 18.6, 17.4, -3.3, -3.6, -4.4, -4.7, -5.1, -5.3. HRMS: $[M+Na]^+$ calculated for $C_{45}H_{69}N_3O_{12}Si_3Na$ 950.40812; found 950.4079.

7-[2-Azido-3,4-di-*O*-acetyl-2-deoxy-α,β-L-fucopyranoside]-14-*O*-*tert*-butyldimethylsilyl-doxorubicinone (84)



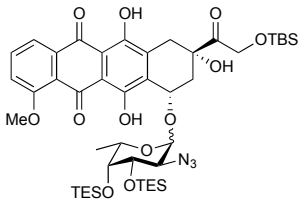
According to general procedure C, glycosyl donor **80** (21.7 mg, 49.2 µmol) was coupled to 14-*O*-TBS-doxorubicinone **23** (22.2 mg, 49.2 µmol, 1 eq). Purification by column chromatography (5:95 EtOAc:pentane - 4:96 – 7:93 acetone:toluene) afforded the title compound as a red solid (20 mg, 25.5 µmol, 52%, 1.5:1 α:β). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 14.15 (s, 1H), 14.08 (s, 1H), 13.25 (s, 1H), 13.22 (s, 1H), 8.04 (dd, *J* = 8.1, 1.0 Hz, 1H), 8.03 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.79 (t, *J* = 8.2 Hz, 2H), 7.78 (t, *J* = 7.9 Hz, 0H), 7.40 (d, *J* = 8.5 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 0H), 5.60 (d, *J* = 4.0 Hz, 1H), 5.58 (t, *J* = 3.1 Hz, 1H), 5.41 (dd, *J* = 3.9, 2.3 Hz, 1H), 5.35 (d, *J* = 3.1 Hz, 1H), 5.13 (d, *J* = 3.4 Hz, 1H), 5.09 (dd, *J* = 11.3, 3.2 Hz, 1H), 4.99 (d, *J* = 20.0 Hz, 1H), 4.91 (app. s, 2H), 4.87 (d, *J* = 20.0 Hz, 0H), 4.86 – 4.82 (m, 1H), 4.62 (s, 1H), 4.34 (q, *J* = 6.6 Hz, 1H), 4.09 (s, 5H), 4.07 (s, 1H), 3.75 (s, 1H), 3.73 – 3.62 (m, 3H), 3.30 – 3.22 (m, 2H), 3.16 (d, *J* = 19.4 Hz, 1H), 3.06 (d, *J* = 19.1 Hz, 1H), 2.57 (d, *J* = 14.8 Hz, 1H), 2.37 – 2.21 (m, 2H), 2.18 (s, 4H), 2.11 (s, 2H), 2.05 (s, 2H), 2.01 (s, 3H), 1.21 (d, *J* = 6.5 Hz, 3H), 0.96 (s, 9H), 0.95 (s, 7H), 0.15 (s, 6H), 0.13 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.6, 211.1, 187.2, 186.9, 186.8, 170.6, 170.5, 169.9, 169.9, 161.2, 161.2, 156.7, 156.4, 155.8, 155.6, 135.9, 135.9, 135.8, 135.7, 135.6, 134.5, 132.9, 132.7, 121.0, 121.0, 120.0, 118.6, 116.1, 114.9, 111.9, 111.7, 111.6, 111.2, 102.4, 99.8, 77.5, 77.1, 77.0, 76.8, 72.0, 70.8, 70.5, 70.5, 69.7, 69.6, 69.5, 68.7, 66.9, 66.8, 65.7, 61.0, 57.4, 56.9, 56.9, 36.1, 35.5, 34.7, 34.5, 26.0, 20.8, 20.8, 18.7, 16.1, 16.1, -5.2, -5.2. HRMS: $[M+Na]^+$ calculated for $C_{37}H_{45}N_3O_{14}SiNa$ 806.2563; found 806.2581.

7-[2-Azido-3,4-*O*-tetraisopropyldisiloxane-2-deoxy-L-fucopyranoside]-14-*O*-tert-butyldimethylsilyldoxorubicinone (85)



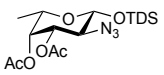
According to general procedure C, glycosyl donor **81** (24 mg, 50 µmol) was coupled to 14-O-*tert*-butyldimethylsilyl-doxorubicinone **23** (40 mg, 80 µmol, 1.5 eq). Column chromatography (1:199 - 50:50 EtOAc:toluene) gave the title compound as a red solid (31 mg, 31 µmol, 68%, 2.6: 1 α:β). Spectral data for the α-anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 14.03 (s, 2H), 13.29 (s, 2H), 8.04 (d, *J* = 7.6 Hz, 2H), 7.78 (t, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 1H), 5.45 (d, *J* = 4.1 Hz, 1H), 5.39 (s, 1H), 5.05 – 4.72 (m, 3H), 4.38 (s, 1H), 4.14 (d, *J* = 2.3 Hz, 1H), 4.13 (s, 1H), 4.11 – 4.10 (m, 1H), 4.09 (s, 3H), 3.61 (dd, *J* = 10.4, 4.0 Hz, 1H), 3.31 – 3.20 (m, 1H), 3.11 (d, *J* = 19.1 Hz, 1H), 2.34 (d, *J* = 14.5 Hz, 2H), 2.26 – 2.14 (m, 1H), 1.32 (d, *J* = 6.4 Hz, 4H), 1.25 (s, 29H), 0.96 (s, 9H), 0.14 (d, *J* = 3.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.2, 187.1, 187.0, 161.2, 156.4, 155.7, 135.8, 135.6, 134.4, 133.2, 121.1, 119.9, 118.6, 111.8, 111.6, 100.3, 77.5, 73.8, 72.9, 69.1, 67.5, 66.8, 60.5, 56.8, 36.0, 34.5, 26.0, 17.7, 17.7, 17.6, 17.4, 17.3, 17.3, 17.2, 17.1, 14.5, 13.9, 13.2, 12.7, -5.3. HRMS: $[M+Na]^+$ calculated for $C_{45}H_{67}N_3O_{13}Si_3Na$ 964.3879; found 964.3871.

7-[2-Azido-3,4-*O*-di-*O*-triethylsilyl-2-deoxy-L-fucopyranoside]-14-*O*-tert-butyldimethylsilyldoxorubicinone (86)



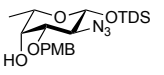
According to general procedure C, glycosyl donor **82** (82 mg, 0.15 mmol) was coupled to 14-O-*tert*-butyldimethylsilyl-doxorubicinone **23** (120 mg, 0.22 mmol, 1.5 eq). Column chromatography (5:95 EtOAc:pentane - 1:400 acetone:toluene) followed by size-exclusion chromatography (Sephadex LH-20, 1:1 DCM:MeOH v/v) of the residue gave the title compound as a red solid (80 mg, 86 µmol, 67%, 2.2: 1 α:β). Spectral data for the α -anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 14.01 (s, 1H), 13.20 (s, 1H), 8.02 – 7.95 (m, 1H), 7.79 – 7.68 (m, 1H), 7.38 (dt, *J* = 8.7, 1.4 Hz, 1H), 5.56 (d, *J* = 3.3 Hz, 1H), 5.40 (dd, *J* = 3.8, 2.3 Hz, 1H), 5.00 – 4.81 (m, 2H), 4.58 (s, 1H), 4.08 (d, *J* = 0.9 Hz, 3H), 3.96 (q, *J* = 6.4 Hz, 1H), 3.78 – 3.66 (m, 3H), 3.58 – 3.47 (m, 1H), 3.43 – 3.33 (m, 1H), 3.29 – 2.95 (m, 2H), 2.33 – 2.11 (m, 2H), 1.26 (d, *J* = 6.3 Hz, 3H), 1.07 – 0.84 (m, 27H), 0.79 – 0.50 (m, 12H), 0.18 – 0.08 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.3, 186.9, 186.8, 161.1, 156.4, 155.7, 135.7, 135.5, 134.5, 133.3, 129.1, 128.3, 125.4, 120.9, 119.8, 118.5, 111.7, 111.5, 99.3, 77.5, 74.9, 71.0, 68.9, 66.6, 60.7, 56.8, 26.0, 17.0, 7.1, 7.0, 5.3, 4.9, -5.2, -5.3. HRMS: $[M+Na]^+$ calculated for $C_{45}H_{69}N_3O_{12}Si_3Na$ 950.4081; found 950.4103.

Thexyldimethylsilyl 3,4-di-*O*-acetyl-2-azido-2-deoxy-β-L-fucopyranoside (87)



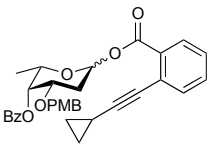
To a solution of fucosyl selenide **76** (2.10 g, 5.10 mmol) in 10:1 MeCN:H_2O (93.5 mL,v/v) was added *N*-iodosuccinimide (1.61 g, 7.14 mmol, 1.4 eq). After stirring for 30 minutes, the resulting solution was diluted with EtOAc and successively washed with 10% aq. $Na_2S_2O_3$ and brine. The combined aqueous layers were then extracted with EtOAc and the resulting combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (5:95 – 20:80 EtOAc:pentane) afforded the intermediate lactol, an orange wax, as a mixture of anomers (1.37 g, 5.00 mmol, 98%, 1:1 α:β). This lactol was then dissolved in DCM (7.6 mL) and after adding imidazole (1.02 g, 15.0 mmol, 3 eq) the solution was stirred for 5 minutes, whereupon thexyldimethylsilyl chloride (1.5 mL, 7.5 mmol, 1.5 eq) was added. After stirring for 2.5 hours, the resulting solution was diluted with DCM and the organic layer successively washed with 1M aq. HCl, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (3:97 EtOAc:pentane) afforded the title compound as a colorless oil (1.99 g, 4.79 mmol, 96%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.15 (dd, *J* = 3.3, 1.0 Hz, 1H), 4.75 (dd, *J* = 10.9, 3.5 Hz, 1H), 4.54 (d, *J* = 7.6 Hz, 1H), 3.72 (q, *J* = 6.4 Hz, 1H), 3.55 (dd, *J* = 10.9, 7.6 Hz, 1H), 2.18 (s, 3H), 2.04 (s, 3H), 1.69 (hept, *J* = 6.9 Hz, 1H), 1.18 (d, *J* = 6.4 Hz, 3H), 0.92 – 0.88 (m, 12H), 0.21 (s, 3H), 0.20 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.6, 170.0, 97.1, 77.5, 77.2, 76.8, 71.4, 69.7, 69.1, 63.4, 33.9, 25.0, 20.8, 20.8, 20.0, 19.9, 18.6, 18.5, 16.2, -2.0, -3.1.

Thexyldimethylsilyl 2-azido-2-deoxy-3-*O*-*p*-methoxybenzyl-β-L-fucopyranoside (88)



To a solution of diacetate **87** (1.87 g, 4.51 mmol) in MeOH (15 mL) was added sodium methoxide (51.7 mg, 0.968 mmol, 0.2 eq). After stirring overnight, the resulting solution was neutralized by the addition of acetic acid and then concentrated *in vacuo*, redissolved in toluene, filtered and concentrated *in vacuo* to afford the crude intermediate diol as a green oil. This diol was then dissolved in toluene (30 mL) together with dibutyltin oxide (1.36 g, 5.46 mmol, 1.2 eq). The resulting solution was stirred for 2.5 hours at 105 °C and successively coevaporated thrice with toluene to afford the *in situ* formed stannylene acetal as a viscous orange oil. The latter was then redissolved in toluene (30 mL) and tetra-*n*-butylammonium bromide (2.18 g, 6.76 mmol, 1.5 eq) and *p*-methoxybenzyl chloride (916 µL, 6.76 mmol, 1.5 eq) were added consecutively. After stirring at 90 °C for 1.5 hours, this was concentrated *in vacuo*, subsequently partitioned between DCM and H_2O and the organic layer dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (5:95 – 10:90 EtOAc:pentane) afforded the title compound as a colorless oil (1.88 g, 4.16 mmol, 92%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.30 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 4.62 (s, 2H), 4.38 (d, *J* = 7.7 Hz, 1H), 3.79 (s, 3H), 3.65 (br.s, 1H), 3.51 – 3.39 (m, 2H), 3.22 (dd, *J* = 10.1, 3.3 Hz, 1H), 2.45 (d, *J* = 2.4 Hz, 1H), 1.66 (hept, *J* = 6.9 Hz, 1H), 1.30 (d, *J* = 6.5 Hz, 3H), 0.91 – 0.86 (m, 12H), 0.18 (s, 3H), 0.17 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5, 129.6, 129.4, 114.0, 96.9, 79.0, 77.5, 77.2, 76.8, 71.7, 70.2, 68.3, 65.1, 55.3, 33.9, 24.9, 20.0, 19.9, 18.5, 18.4, 16.5, -1.9, -3.3. HRMS: $[M+Na]^+$ calculated for $C_{22}H_{37}N_3O_5SiNa$ 474.62822; found 474.2405.

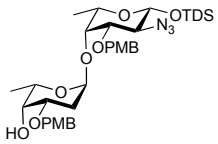
***o*-Cyclopropylethynylbenzoyl 4-*O*-benzoyl-2-deoxy-3-*O*-*p*-methoxybenzyl-α,β-L-fucopyranoside (89)**



To a solution of thiofucoside **34** (929 mg, 2.00 mmol) in 10:1 MeCN:H_2O (34.2 mL, v/v) was added *N*-iodosuccinimide (540 mg, 2.40 mmol, 1.2 eq). After stirring for 1 hour, the resulting solution was diluted with EtOAc and successively washed with 10% aq. $Na_2S_2O_3$ and brine. The combined aqueous layers were then extracted with EtOAc and the resulting combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude intermediate lactol as a yellow oil. The hemi-acetal was esterified with *ortho*-cyclopropylethynyl benzoic acid **20** according to general procedure B. Purification by column chromatography (5:95 – 20:80 EtOAc:pentane) afforded the title compound as a yellow oil (912 mg, 1.69 mmol, 84%, 1:2.5 α:β). Spectral data for the α and β anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.20 – 8.16 (m, 2H), 8.16 – 8.13 (m, 1H), 8.00 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.86 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.62 – 7.55 (m, 2H), 7.53 – 7.40 (m, 6H), 7.35 – 7.28 (m, 2H), 7.24 – 7.17 (m, 3H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 8.6 Hz, 1H), 6.63 (d, *J* = 2.3 Hz, 1H), 6.03 – 5.95 (m, 1H), 5.67 (app. br. s, 1H), 5.54 (app. d, *J* = 2.5 Hz, 1H), 4.76 (d, *J* = 10.8 Hz, 1H), 4.70 (d, *J* = 11.5 Hz, 1H), 4.46 (d, *J* = 11.6 Hz, 1H), 4.43 (d, *J* = 10.8 Hz, 1H), 4.42 – 4.38 (m, 1H), 4.29 – 4.19 (m, 1H), 3.89 (qd, *J* = 6.5, 0.8 Hz, 1H), 3.79 (s, 4H), 3.78 – 3.76 (m, 1H), 3.75 (s, 1H), 2.34 (ddd, *J* = 13.6, 9.1, 3.7 Hz, 1H), 2.24 – 2.14 (m, 3H), 1.51 (tt, *J* = 7.8, 5.3 Hz, 1H), 1.43 (tt, *J* = 8.1, 5.2 Hz, 1H), 1.32 (d, *J* = 6.4 Hz, 3H), 1.26 (d, *J* = 6.5 Hz, 1H), 0.94 – 0.88 (m, 4H), 0.88 – 0.85 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 165.0, 164.5, 159.4, 159.4, 134.8, 134.4, 133.3, 133.3, 132.2, 132.0, 130.9,

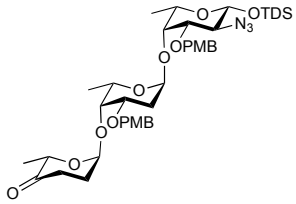
130.8, 130.8, 130.1, 130.0, 130.0, 129.9, 129.9, 129.6, 129.5, 128.6, 128.5, 127.4, 127.1, 125.2, 124.6, 114.0, 113.9, 100.1, 99.9, 93.8, 93.2, 77.5, 76.8, 75.1, 74.6, 73.6, 71.2, 71.1, 70.2, 70.1, 69.3, 68.5, 68.3, 55.4, 55.4, 32.4, 30.7, 17.2, 16.9, 9.1, 9.1, 9.1, 9.0, 0.8, 0.8. HRMS: $[M+Na]^+$ calculated for $C_{33}H_{32}O_7Na$ 563.20402; found 563.2048.

Thexyldimethylsilyl 2-deoxy-3-*O*-*p*-methoxybenzyl-α-L-fucopyranosyl-(1→4)-2-azido-2-deoxy-3-*O*-*p*-methoxybenzyl-β-L-fucopyranoside (90)



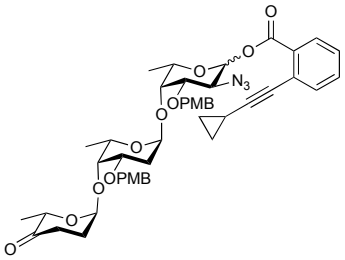
Method 1: Acceptor **88** (0.905 g, 2.00 mmol) and donor **34** (1.30 g, 2.81 mmol, 1.4 eq) were coevaporated thrice with toluene and then dissolved in DCM (25 mL), after which activated 4 Å molecular sieves were added and stirred for 30 minutes. This solution was then cooled to -78 °C, whereupon *N*-iodosuccinimide (631 mg, 2.81 mmol, 1.4 eq) and trifluoromethanesulfonic acid (52.8 µL 0.601 mmol, 0.3 eq) were added consecutively. After stirring for 30 minutes, the solution was allowed to warm up to -40 °C over the course of 30 minutes and was subsequently neutralized by the dropwise addition of triethylamine (646 µL) while stirring commenced for 10 minutes. Hereafter, the resulting solution was filtered, diluted with $CHCl_3$ and the organic layer successively washed with 10% aq. $Na_2S_2O_3$ and H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (7:93 EtOAc:pentane) afforded the protected α-disaccharide (509 mg, 0.632 mmol, 32%) and an inseparable α:β mixture (1:2.2 α:β, 429 mg, 0.532 mmol, 26%) as colorless oils. *Method 2:* Acceptor **88** (45.2 mg, 0.1 mmol) and donor **89** (75.7 mg, 0.14 mmol, 1.4 eq, 1:2.5 α:β) were coevaporated thrice with toluene and then dissolved in DCM (2 mL), after which activated 4 Å molecular sieves were added, and stirred for 30 minutes. This solution was then cooled to -78 °C, whereupon freshly prepared PPh_3AuNTf_2 (0.1 M solution in DCM, 0.1 mL, 0.01 mmol, 0.1 eq) was added. After stirring overnight while warming up to ambient temperature, the resulting solution was filtered and concentrated *in vacuo*. Purification by column chromatography (6:94 -10:90 EtOAc:pentane) afforded the protected α-disaccharide as a colorless oil (67.9 mg, 0.084 mmol, 84%, 14:1 α:β). Spectral data for the α anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.13 – 8.07 (m, 2H), 7.55 (tt, *J* = 7.4, 1.3 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 2H), 7.33 (d, *J* = 8.6 Hz, 2H), 7.23 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 5.55 (br. s, 1H), 5.10 (d, *J* = 2.6 Hz, 1H), 4.80 – 4.71 (m, 2H), 4.62 (d, *J* = 12.2 Hz, 1H), 4.56 (q, *J* = 6.5 Hz, 1H), 4.41 (d, *J* = 11.2 Hz, 1H), 4.38 (d, *J* = 7.6 Hz, 1H), 4.13 (ddd, *J* = 9.1, 6.5, 2.7 Hz, 1H), 3.80 (s, 3H), 3.79 (d, *J* = 3.1 Hz, 1H), 3.75 (s, 3H), 3.52 (dd, *J* = 10.6, 7.6 Hz, 1H), 3.40 (q, *J* = 6.4 Hz, 1H), 3.16 (dd, *J* = 10.6, 3.1 Hz, 1H), 2.18 – 2.09 (m, 2H), 1.70 (hept, *J* = 6.7 Hz, 1H), 1.23 (d, *J* = 6.5 Hz, 3H), 1.02 (d, *J* = 6.5 Hz, 3H), 0.93 – 0.89 (m, 12H), 0.20 (s, 3H), 0.19 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.4, 159.4, 159.3, 133.0, 130.3, 130.2, 129.9, 129.8, 129.7, 129.2, 128.4, 113.9, 113.9, 100.0, 97.3, 77.8, 77.5, 76.8, 75.0, 71.7, 71.4, 70.8, 70.1, 69.9, 65.9, 65.5, 55.4, 55.3, 34.0, 31.6, 25.1, 20.2, 20.1, 18.6, 18.6, 17.3, 17.1, -1.8, -2.7. HRMS: $[M+Na]^+$ calculated for $C_{43}H_{59}N_3O_{10}SiNa$ 828.38619; found 828.3885. To a solution of the above disaccharide benzoate (467 mg, 0.579 mmol) in MeOH (23 mL) and DCM (3 mL) was added sodium methoxide (0.50 g, 9.26 mmol, 16 eq) portion wise over the duration of 3 weeks, whereupon the resulting solution was neutralized by the dropwise addition of AcOH. The solution was then concentrated *in vacuo*, redissolved in DCM, filtered and concentrated *in vacuo*. Purification by column chromatography (10:90 – 40:60 EtOAc:pentane) afforded the title compound as a colorless oil (256 mg, 0.365 mmol, 63%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 (d, *J* = 8.6 Hz, 2H), 7.29 (d, *J* = 8.6 Hz, 2H), 6.92 – 6.85 (m, 4H), 4.98 (d, *J* = 3.4 Hz, 1H), 4.75 (d, *J* = 12.3 Hz, 1H), 4.58 (d, *J* = 12.2 Hz, 1H), 4.54 (s, 2H), 4.37 (d, *J* = 7.6 Hz, 1H), 4.32 (q, *J* = 6.6 Hz, 1H), 3.96 (ddd, *J* = 11.9, 4.9, 2.9 Hz, 1H), 3.80 (s, 3H), 3.80 (s, 3H), 3.76 – 3.73 (m, 2H), 3.49 (dd, *J* = 10.6, 7.6 Hz, 1H), 3.37 (q, *J* = 6.4 Hz, 1H), 3.12 (dd, *J* = 10.6, 3.1 Hz, 1H), 2.20 (s, 1H), 2.08 (dd, *J* = 12.6, 5.0 Hz, 1H), 1.94 (td, *J* = 12.3, 3.7 Hz, 1H), 1.69 (hept, *J* = 6.9 Hz, 1H), 1.21 (d, *J* = 6.4 Hz, 3H), 1.14 (d, *J* = 6.6 Hz, 3H), 0.93 – 0.87 (m, 12H), 0.19 (s, 3H), 0.18 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5, 159.3, 130.1, 129.8, 129.6, 129.2, 114.0, 113.9, 99.7, 97.2, 77.8, 77.5, 76.8, 74.6, 72.6, 71.4, 70.8, 69.9, 68.5, 66.1, 65.4, 55.3, 55.3, 34.0, 29.8, 25.0, 20.1, 20.1, 18.6, 18.6, 17.3, 17.0, -1.8, -2.8. HRMS: $[M+Na]^+$ calculated for $C_{36}H_{55}N_3O_9SiNa$ 724.35998; found 724.3614.

Thexyldimethylsilyl 2,3-dideoxy-4-ulo-α-L-fucopyranosyl-(1→4)-2-deoxy-3-*O*-*p*-methoxybenzyl-α-L-fucopyranosyl-(1→4)-2-azido-2-deoxy-3-*O*-*p*-methoxybenzyl-β-L-fucopyranoside (91)



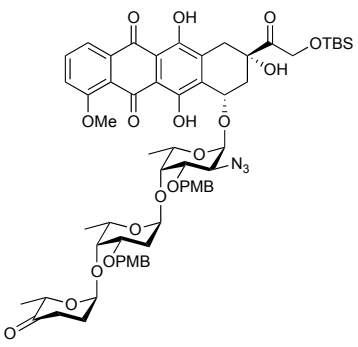
Acceptor disaccharide **90** (246 mg, 0.351 mmol) and donor **35** (161 mg, 0.491 mmol, 1.4 eq) were coevaporated thrice with toluene and then dissolved in 4:1 Et_2O:DCE (4 mL, v/v), after which activated 4 Å molecular sieves were added, and stirred for 1 hour. This solution was then cooled to 10 °C, whereupon iodonium di-*sym*-collidine perchlorate (658 mg, 1.40 mmol, 4 eq) was added. After stirring for 1 hour, the resulting solution was filtered, diluted with Et_2O and successively washed with 10% aq. $Na_2S_2O_3$, 1M aq. $CuSO_4$ and H_2O. The combined aqueous layers were then extracted with Et_2O and the resulting combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (6:94 – 10:90 EtOAc:pentane), followed by size-exclusion chromatography (Sephadex LH-20, eluent 1:1 DCM:MeOH), afforded the crude protected trisaccharide. To a solution of this crude trisaccharide benzoate in MeOH (3 mL) and DCM (1 mL) was added sodium methoxide (72 mg, 1.37 mmol, 4.3 eq). After stirring for 3 days, the resulting solution was neutralized by the dropwise addition of acetic acid and concentrated *in vacuo*. Purification by column chromatography (10:90 – 40:60 EtOAc:pentane) afforded the trisaccharide as a white crystalline solid (208 mg, 0.255 mmol, 80% over 2 steps). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 – 7.27 (m, 4H), 6.91 – 6.84 (m, 4H), 5.02 (d, *J* = 2.6 Hz, 1H), 4.85 (d, *J* = 3.2 Hz, 1H), 4.71 (d, *J* = 12.2 Hz, 1H), 4.61 (d, *J* = 11.8 Hz, 1H), 4.58 (d, *J* = 12.2 Hz, 1H), 4.53 (d, *J* = 11.8 Hz, 1H), 4.41 (q, *J* = 6.5 Hz, 1H), 4.37 (d, *J* = 7.6 Hz, 1H), 4.22 (q, *J* = 6.5 Hz, 1H), 3.91 (td, *J* = 8.6, 2.4 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.74 (s, 1H), 3.73 (s, 1H), 3.51 (s, 1H), 3.44 (dd, *J* = 10.6, 7.6 Hz, 1H), 3.36 (q, *J* = 6.4 Hz, 1H), 3.10 (dd, *J* = 10.6, 3.1 Hz, 1H), 2.13 – 2.02 (m, 3H), 1.92 (tt, *J* = 13.3, 4.0 Hz, 1H), 1.76 – 1.62 (m, 4H), 1.21 (d, *J* = 6.4 Hz, 3H), 1.00 (d, *J* = 6.5 Hz, 3H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.91 – 0.87 (m, 12H), 0.18 (s, 3H), 0.17 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 159.1, 130.6, 129.7, 129.2, 129.0, 113.8, 113.7, 99.7, 98.5, 97.1, 77.7, 77.5, 76.8, 75.4, 74.2, 72.2, 71.3, 70.7, 69.8, 67.8, 67.5, 66.4, 65.4, 55.2, 33.9, 30.5, 29.7, 25.8, 24.9, 23.5, 20.1, 18.5, 17.5, 17.2, 17.1, -1.9, -2.8. HRMS: $[M+Na]^+$ calculated for $C_{42}H_{65}N_3O_{11}SiNa$ 838.42806; found 838.4315. To a solution of the above trisaccharide alcohol (208 mg, 0.255 mmol) in DCM (21.5 mL), $NaHCO_3$ (771 mg, 9.18 mmol, 36 eq) and Dess-Martin periodinane (260 mg, 0.612 mmol, 2.4 eq) were added consecutively. After stirring for 2 hours, 10% aq. $Na_2S_2O_3$ and sat. aq. $NaHCO_3$ were added and vigorous stirring of the resulting biphasic mixture commenced for 1 hour, whereupon the organic layer was separated and the aqueous layer extracted thrice with DCM. The resulting combined organic layers were then successively washed with 10% aq. $Na_2S_2O_3$ and sat. aq. $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (10:90 – 30:70 EtOAc:pentane) afforded the title compound as a thick colorless oil (166 mg, 0.204 mmol, 80%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.31 (d, *J* = 8.6 Hz, 2H), 7.27 (d, *J* = 8.6 Hz, 2H), 6.91 – 6.85 (m, 4H), 5.06 – 4.99 (m, 2H), 4.76 – 4.67 (m, 2H), 4.62 – 4.55 (m, 2H), 4.53 (d, *J* = 11.6 Hz, 1H), 4.38 (d, *J* = 7.6 Hz, 1H), 4.27 (q, *J* = 6.4 Hz, 1H), 3.94 (ddd, *J* = 12.0, 4.6, 2.7 Hz, 1H), 3.84 (d, *J* = 2.5 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.74 (d, *J* = 3.1 Hz, 1H), 3.46 (dd, *J* = 10.6, 7.6 Hz, 1H), 3.37 (q, *J* = 6.4 Hz, 1H), 3.12 (dd, *J* = 10.6, 3.1 Hz, 1H), 2.60 (ddd, *J* = 15.2, 9.0, 5.8 Hz, 1H), 2.39 (ddd, *J* = 15.9, 7.6, 5.7 Hz, 1H), 2.27 (ddd, *J* = 14.0, 9.3, 4.8 Hz, 1H), 2.19 (dddd, *J* = 9.9, 7.6, 5.9, 2.7 Hz, 1H), 2.11 (dd, *J* = 12.3, 4.4 Hz, 1H), 2.02 (td, *J* = 12.1, 3.7 Hz, 1H), 1.67 (hept, *J* = 6.9 Hz, 1H), 1.22 (d, *J* = 6.4 Hz, 3H), 1.03 (d, *J* = 6.5 Hz, 3H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.92 – 0.87 (m, 12H), 0.19 (s, 3H), 0.18 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.4, 159.3, 159.3, 130.5, 129.8, 129.4, 129.1, 113.9, 99.9, 97.8, 97.2, 77.8, 77.5, 76.8, 75.7, 74.6, 72.1, 71.8, 71.5, 70.8, 70.0, 67.6, 65.5, 55.4, 34.1, 34.0, 30.5, 29.8, 29.6, 25.0, 20.1, 20.1, 18.6, 18.6, 17.5, 17.3, 14.8, -1.8, -2.7. HRMS: $[M+Na]^+$ calculated for $C_{42}H_{63}N_3O_{11}SiNa$ 836.41241; found 836.4141.

***o*-Cyclopropylethynylbenzoyl 2,3-dideoxy-4-ulo-α-L-fucopyranosyl-(1→4)-2-deoxy-3-*O*-*p*-methoxybenzyl-α-L-fucopyranosyl-(1→4)-2-azido-2-deoxy-3-*O*-*p*-methoxybenzyl-L-fucopyranoside (92)**



To an ice-cooled solution of trisaccharide **91** (155 mg, 0.191 mmol) in pyridine (3.66 mL) and THF (7.63 mL), HF.pyr complex (70 wt% HF, 1.83 mL) was added dropwise. After stirring overnight while warming up to ambient temperature, the resulting solution was diluted with H_2O and the aqueous layer extracted with EtOAc. The organic layer was then successively washed with 1M aq. $CuSO_4$ and H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (40:60 – 50:50 EtOAc:pentane) afforded the intermediate lactol. The hemi-acetal was esterified with *ortho*-cyclopropylethynyl benzoic acid **20** according to general procedure B. Purification by column chromatography (5:95 – 30:70 EtOAc:pentane) afforded title β benzoate (39 mg, 46.4 µmol, 26%) and an inseparable α/β mixture (32 mg, 38.1 µmol, 22%, 2.1:1 α:β) as light yellow oils. Spectral data for the β anomer: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.03 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.50 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.44 (td, *J* = 7.5, 1.4 Hz, 1H), 7.36 – 7.27 (m, 5H), 6.92 – 6.86 (m, 4H), 5.60 (d, *J* = 8.5 Hz, 1H), 5.07 (d, *J* = 2.8 Hz, 1H), 5.04 (app. t, *J* = 4.3 Hz, 1H), 4.78 (d, *J* = 12.1 Hz, 1H), 4.69 (q, *J* = 6.7 Hz, 1H), 4.66 – 4.61 (m, 2H), 4.54 (d, *J* = 11.5 Hz, 1H), 4.30 (q, *J* = 6.4 Hz, 1H), 3.97 (ddd, *J* = 11.8, 4.9, 2.6 Hz, 1H), 3.90 (d, *J* = 2.6 Hz, 1H), 3.86 (d, *J* = 3.0 Hz, 1H), 3.82 (s, 3H), 3.82 – 3.80 (m, 1H), 3.75 (s, 3H), 3.65 (q, *J* = 6.5 Hz, 1H), 3.37 (dd, *J* = 10.5, 3.0 Hz, 1H), 2.61 (ddd, *J* = 15.2, 9.0, 5.8 Hz, 1H), 2.40 (ddd, *J* = 15.6, 7.4, 5.5 Hz, 1H), 2.27 (app. td, *J* = 8.9, 4.6 Hz, 1H), 2.20 (app. ddt, *J* = 10.2, 6.2, 2.6 Hz, 1H), 2.13 – 2.09 (m, 1H), 2.05 (dd, *J* = 12.0, 3.9 Hz, 1H), 1.51 (tt, *J* = 7.5, 5.8 Hz, 1H), 1.29 (d, *J* = 6.5 Hz, 3H), 1.07 (d, *J* = 6.5 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.91 – 0.87 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.2, 164.0, 159.5, 159.3, 134.5, 132.4, 130.8, 130.4, 130.2, 129.3, 129.2, 127.1, 125.6, 114.0, 113.9, 100.2, 100.0, 98.0, 93.6, 78.3, 77.5, 76.8, 75.5, 74.5, 74.1, 72.3, 72.2, 71.9, 71.7, 70.1, 67.7, 62.0, 55.4, 55.3, 34.1, 30.6, 29.6, 17.5, 17.1, 14.9, 9.1, 9.0, 0.9. HRMS: $[M+Na]^+$ calculated for $C_{46}H_{53}N_3O_{12}Na$ 862.35214; found 862.3541.

7-[2,3-Dideoxy-4-ulo-α-L-fucopyranosyl-(1→4)-2-deoxy-3-*O*-*p*-methoxybenzyl-α-L-fucopyranosyl-(1→4)-2-azido-2-deoxy-3-*O*-*p*-methoxybenzyl-α-L-fucopyranoside]-14-*O*-*tert*-butyldimethylsilyl-doxorubicinone (93)



According to general procedure C, glycosyl donor **92** (18.0 mg, 21.4 µmol, 1:1.5 α:β) was coupled to 14-O-TBS-doxorubicinone **23** (13.6 mg, 25.7 µmol, 1.2 eq). Purification by column chromatography (20:80 EtOAc:pentane then 2:98 – 100:0 acetone:toluene) afforded a red amorphous solid (12.0 mg, 10.2 µmol, 47%, >7.7:1 α:β). A second purification by column chromatography (2:98 – 10:90 acetone:toluene) afforded the title compound as a red amorphous solid (10 mg, 8.5 µmol, 40%). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 14.08 (s, 1H), 13.28 (s, 1H), 8.04 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.78 (t, *J* = 8.1 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.26 – 7.22 (m, 4H), 6.89 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 5.53 (d, *J* = 3.2 Hz, 1H), 5.39 (t, *J* = 3.1 Hz, 1H), 5.05 (t, *J* = 2.6 Hz, 1H), 5.01 (t, *J* = 4.2 Hz, 1H), 4.88 (d, *J* = 19.9 Hz, 1H), 4.84 (d, *J* = 19.9 Hz, 1H), 4.70 (d, *J* = 11.6 Hz, 1H), 4.68 (q, *J* = 6.6 Hz, 1H), 4.60 (d, *J* = 11.9 Hz, 1H), 4.54 (d, *J* = 11.6 Hz, 1H), 4.52 (d, *J* = 11.9 Hz, 1H), 4.18 (q, *J* = 6.4 Hz, 1H), 4.18 (s, 1H), 4.09 (s, 3H), 3.99 (q, *J* = 6.6 Hz, 1H), 3.94 (br. s, 1H), 3.87 (ddd, *J* = 13.0, 6.6, 3.3 Hz, 1H), 3.84 (d, *J* = 3.0 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.59 – 3.54 (m, 2H), 3.23 (dd, *J* = 19.0, 1.7 Hz, 1H), 3.09 (d, *J* = 18.9 Hz, 1H), 2.59 (ddd, *J* = 15.1, 9.0, 5.8 Hz, 1H), 2.39 (ddd, *J* = 15.7, 7.4, 5.5 Hz, 1H), 2.28 – 2.22 (m, 2H), 2.24 – 2.19 (m, 1H), 2.20 – 2.13 (m, 1H), 2.07 – 2.01 (m, 2H), 1.27 (d, *J* = 6.6 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.96 (s, 9H), 0.96 – 0.93 (m, 3H), 0.15 (s, 3H), 0.14 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 211.3, 211.1, 187.2, 187.0, 161.2, 159.4, 159.3, 156.4, 155.7, 135.9, 135.7, 134.4, 133.2, 130.4, 129.5, 129.3, 129.1, 121.2, 120.0, 118.6, 114.0, 113.9, 111.9, 111.7, 100.0, 99.8, 97.9, 77.4, 76.9, 75.5, 75.2, 74.8, 72.2, 71.9, 71.6, 70.1, 68.9, 68.1, 67.8, 66.7, 59.2, 56.9, 55.5, 55.4, 36.0, 34.5, 34.1, 32.1, 31.6, 30.7, 30.5, 29.9, 29.6, 26.0, 22.8, 18.7, 17.4, 17.3, 14.9, 14.3, 0.1, -5.1, -5.3. HRMS: $[M+Na]^+$ calculated for $C_{61}H_{75}N_3O_{19}SiNa$ 1204.46562; found 1204.4666.

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Nederlandse samenvatting

Sinds zijn isolatie in 1969, is de anthracycline doxorubicine een van de meest gebruikte anti-kanker medicijnen geworden, ondanks zijn cardiotoxiciteit. Meer dan duizend analoga zijn geïsoleerd uit de natuur en geprepareerd middels organische synthese, maar de overgrote meerderheid van deze verbindingen overtrof doxorubicine niet uitgaande van zijn effectiviteit en cardiotoxiciteit. De uitzondering bleek aclarubicine, welke veel minder cardiotoxisch is, echter deze nauw verwante structurele analoog wordt momenteel niet buiten China en Japan in de kliniek gebruikt. Het is onlangs aangetoond dat zowel doxorubicine als aclarubicine de eigenschap heeft om de evictie van histonen uit chromatine te induceren, en het is tevens gehypothetiseerd dat dit het belangrijkste werkingsmechanisme is achter anti-tumor activiteit.

Het werk beschreven in deze Thesis omvat de synthese van anthracyclines die zijn geïnspireerd door de structuren van doxorubicine en aclarubicine, met het doel om structuur-activiteitsrelaties voor deze verbindingen vast te stellen. Daartoe zijn hybride structuren geprepareerd, gekarakteriseerd door structurele elementen uit beide anthracyclines, alsmede regio-isomeren, stereo-isomeren en andere derivaten van doxorubicine. Deze zouden uiteindelijk het design van anthracyclines met verminderde cardiotoxiciteit en betere effectiviteit mogelijk moeten maken.

Hoofdstuk 1 biedt een historisch overzicht van de ontdekking van de eerste anthracyclines en hun gebruik in de behandeling van kanker, en belicht ook een aantal relevante synthetische routes van 2-deoxyglycosides en anthracyclines.

Studies naar de synthese van *N,N*-dimethyldoxorubicin zijn beschreven in **Hoofdstuk 2**. Deze hybride anthracycline combineert structurele elementen uit doxorubicine en aclarubicine. Gezien directe reductieve alkylering van de amine in (partieel beschermd) doxorubicine leidde tot ongewenste reductieve van het de keton functionele groep, een nieuwe strategie moest worden ontwikkeld welke zich baseert op de glycosylering van een op de juiste wijze beschermd anthracycline aglycon met een orthogonaal beschermde *ortho*-alkynylbenzoaat glycosyl donor middels de goud(I)-glycosyleringschemie ontwikkeld door de groep van Yu. Deze strategie wierp zijn vruchten af, en de goud-geïnduceerde glycosylering verliep in uitstekende α-stereoselectiviteit. De keuze voor een 4'-triethylsilyl beschermgroep

faciliteerde de reductieve alkylering terwijl het keton intact bleef, en uiteindelijke ontscherming gaf *N,N*-dimethyldoxorubicine.

Hoofdstuk 3 beschrijft de synthese van een reeks van negen doxorubicine /aclarubicine hybride structuren die de chemische ruimte tussen deze twee anthracyclines opvullen. De assemblage van deze verbindingen was mogelijk door het gebruik van Yu's *ortho*-alkynylbenzoaat glycosyleringsmethode die in Hoofdstuk 2 was verkend om de α-glycosidische band tussen het respectievelijke aglycon en de mono-/di-/trisaccharide groepen te construeren. De relevante di- en trisaccharide donoren werden in elkaar gezet middels (iteratieve) α-selectieve IDCP-gemediëerde glycosyleringsreacties, en de anthracycline aglyconen warden verkregen uit zure hydrolyse van de oorspronkelijke geneesmiddelen. Verdere aandachtspunten in deze syntheses zijn de orthogonale verwijdering van het anomere *p*-methoxyfenolaat in de aanwezigheid van de PMB-groep present op de oliose functie, en de introductie van de dimethylamine functie *na* de glycosylering.

Hoofdstuk 4 beschrijft de synthese van een serie analoga van doxorubicine die zich onderscheiden in de aard van de functionaliteit op de 3'-positie. Deze omvatten neutral 3'-analoga (de basische amine ontbrekend), 3'-methyl analoga die een sterische factor op de daunosamine ring introduceren, enkelvoudig *N*-gemethyleerd en dubbel *N*-geëthyleerd doxorubicine en om af te sluiten *N*-heterocyclische doxorubicines. De laatstgenoemde verbindingen werden verkregen uit een enkele reactie uit doxorubicine, waar de andere verbindingen geassembleerd werden vanuit de relevante *ortho*-alkynylbenzoaat donoren en beschermd doxorubicinone. In plaats van de glycosides te prepareren via deoxygenering en aminering van L-fucose of L-rhamnose, kunnen sommige zeldzame suikers ook verkregen worden uit natuurlijke bron, een strategie toegepast voor de synthese van de 3'-methyl doxorubicines. Methanolyse van vancomycine faciliteerde de isolatie van zijn suikergroep vancosamine, welke naar wens gefunctionaliseerd en aan het doxorubicinone aglycon aangehecht kon worden.

Hoofdstuk 5 beschrijft de synthese van stereo- en regio isomeren met betrekking tot de aminosuiker functie van doxorubicine. Epimeren van de 3'- en 4'-positie zijn geprepareerd, samen met hun *N,N*-gedimethyleerde varianten. Daarnaast gaf het verwisselen van de 3'- en 4'-positie twee *iso*-doxorubicines.

List of publications

Doxorubicin and Aclarubicin: Shuffling anthracycline glycans for improved cytotoxic agents
D.P.A. Wander, S.Y. van der Zanden, J.J.C Neefjes, G.A. van der Marel, H.S. Overkleeft, J.D.C. Codée
Manuscript in preparation

Uncoupling DNA damage from chromatin damage towards detoxifying doxorubicin
X. Qiao*, S.Y. van der Zanden*, D.P.A. Wander, D.M. Borràs, O. van Tellingen, J.-Y. Song, N. van Gils, A. Rutten, E. Giacomelli, M. Bellin, V. Orlova, J.M. Bakker, M.P. Snyder, C.L. Zuur, B. Pang, C.L. Mummery, L. Smit, H.S. Overkleeft and J.J.C. Neefjes
Manuscript in preparation

Immunoproteasome inhibitor-doxorubicin conjugates target Multiple Myeloma cells and release Doxorubicin upon low-dose photon irradiation
E. Maurits*, M.J. van de Graaff*, S. Maiorana, D.P.A. Wander, S.Y. van der Zanden, B.I. Florea, J.J.C. Neefjes, G.A. van der Marel, H.S. Overkleeft, S.I. van Kasteren
Manuscript in preparation

Defining the S_N1 side of glycosylation reactions: stereoselectivity of glycopyranosyl cations
T. Hansen, L. Lebedel, W. A. Remmerswaal, S. van der Vorm, D. P. A. Wander, M. Somers, H. S. Overkleeft, D. V Filippov, J. Désiré, A. Mingot, Y. Bleriot, G. A. van der Marel, S. Thibaudeau and J. D. C. Codée
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J. Am. Chem. Soc., **2017**, 139, 6534–6537.

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Curriculum Vitae

Dennis Wander was born in Spijkenisse on the 18th of August, 1991. He finished his high school (VWO) at Penta College CSG Angelus Merula in that city in 2009, after which he started the bachelor of Molecular Science and Technology in Leiden. Upon completion of his bachelor thesis in 2012, entitled "ω-azido-sphinganine: a tool to study (glyco)-sphingolipid metabolism", he received his degree. After this, he started his master's in Chemistry at Leiden University, trajectory 'Design and Synthesis'. Two internships were performed during this time, "Design, synthesis and biological evaluation of (non)-symmetrical 2-amino-4,6-diaryl-1,3,5-triazines as long residence time A_1 antagonists – a hybrid scaffold approach" in the group of prof. dr. A.P. IJzerman at the LACDR, and "Synthesis of potential cyclophellitol- cyclopropane based covalent and non-covalent inhibitors for retaining α- and β-glucosidase" in the group of prof. dr. H.S. Overkleeft at the Bio-Organic Synthesis group at Leiden University. In late 2014, he started his PhD in that same group. Parts of the research described in this Thesis were presented on posters at CHAINS (Veldhoven, 2015, 2016, 2017), Chemical Immunology Conference (Amsterdam, 2015 - 2019), Reedijk Symposium (2017) and the European Carbohydrate Symposium (Barcelona, 2017). Oral presentations of this work were given at the Chemical Immunology Conference (Amsterdam, 2017), KNCV Organic Chemistry Symposium (Wageningen, 2017), the World Carbohydrate Symposium (Lisbon, 2018) and the European Carbohydrate Symposium (Leiden, 2019). Dennis is currently continuing his research in the group of prof. dr. H.S. Overkleeft as a postdoctoral fellow.

Nawoord

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